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ABSTRACT
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(54) PHENOXY-HYDROXYPROPYLAMINES

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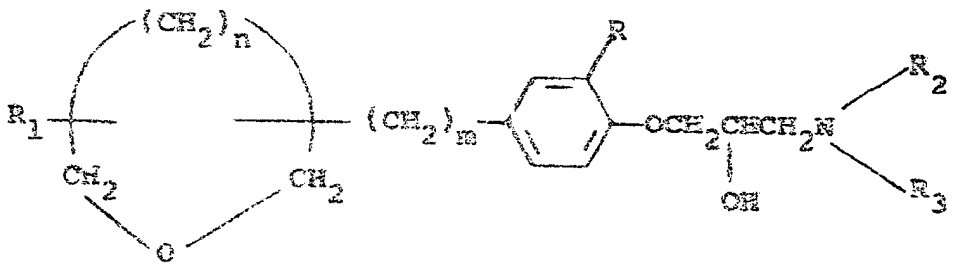
(74) BI

(57) The new compounds according to the invention possess valuable pharmacological activities and can be used in therapy as a β-adrenergic cardioselective blocking agent.

CLAIM 1. A compound having the general formula:



I

in which

R_1 represents a hydrogen atom, a lower alkyl radical or a lower cycloalkyl radical.

R_2 and R_3 each represent a straight-chain or branched lower alkyl radical, or the dimethoxyphenylethyl or phenylisopropyl radical.

R_3 can also be a hydrogen atom.

.../2

R represents a hydrogen or halogen atom, or a lower alkyl, lower alkoxy, lower cycloalkyl, nitro, allyl or acetyl group,

n is equal to two or three, and

m is equal to zero, one, two or three,

and pharmaceutically acceptable non-toxic acid addition salts thereof.

COMMONWEALTH OF AUSTRALIA

Patents Act 1952- 1976

CONVENTION APPLICATION FOR A PATENT

~~X~~We HEXACHIMIE a Body Corporate organized and existing under the laws of France, of 128, rue Danton, 92504 Rueil-Malmaison, France,

hereby apply for the grant of a Patent for an invention entitled

"New Phenoxy-Hydroxypropylamines and Methods For Their Preparation",

which is described in the accompanying ~~provisional~~ complete specification.

This application is made under the provisions of Part XVI of the Patents Act 1952~~7~~6 and is based on an application for a patent or similar protection made

in	England	on 22nd July, 1976 (30 647)
in	England	on 22nd December, 1976 (53 576)

~~X~~Our address for service is: F. B. Rice & Co., 101 Mort St., Balmain, NSW 2041

Dated this 18th day of JULY, 1977

HEXACHIMIE.

by

Patent Attorney

F. B. RICE & CO.,
Patent Attorneys,
Sydney.

To: The Commissioner of Patents,
Commonwealth of Australia.

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1976

COMPLETE SPECIFICATION

(ORIGINAL)

Class Int. Class

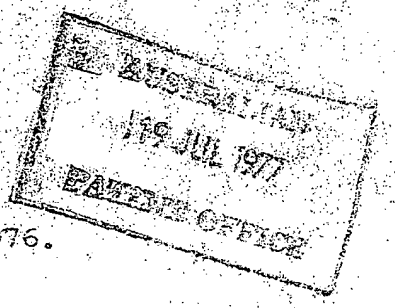
Application Number :

Lodged :

Complete Specification Lodged :

Accepted :

Published :



Priorities : 22nd July, 1976
22nd December, 1976.

Related Art :

Name of Applicant : Hexachimie.

Address of Applicant : 128, rue Danton,
92504 Rueil-Malmaison,
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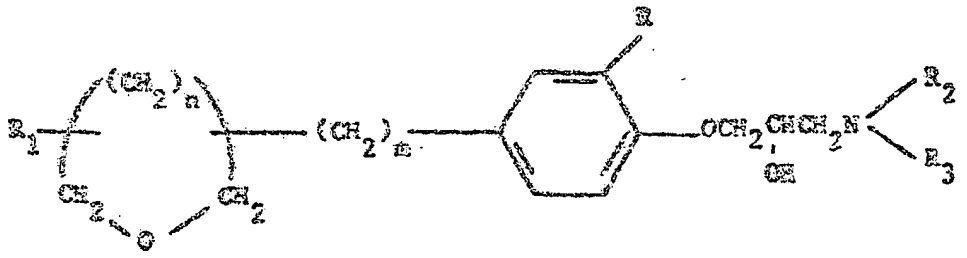
Actual Inventor :
Jean-Marie Teulon.

Address for Service : F.B. RICE & CO.,
Patent Attorneys,
The Forth and Clyde,
101 Mort Street,
BALMAIN. 2041.

Complete Specification for the invention entitled:
"New Phenoxy-Hydroxypropylamines and Methods For Their Preparation".

The following statement is a full description of this invention including the best method of performing it known to us :-

The present invention relates to new derivatives of phenoxy-hydroxypropylamine of the general formula I:



I

in which

R_1 represents a hydrogen atom, a lower alkyl radical or a lower cycloalkyl radical,

R_2 and R_3 each represent a straight-chain or branched lower alkyl radical, or the dimethoxyphenylethyl or phenylisopropyl radical,

R_3 can also be a hydrogen atom,

R represents a hydrogen or halogen atom, or a lower alkyl, lower alkoxy, lower cycloalkyl, nitro, allyl or acetyl group,

n is equal to two or three, and

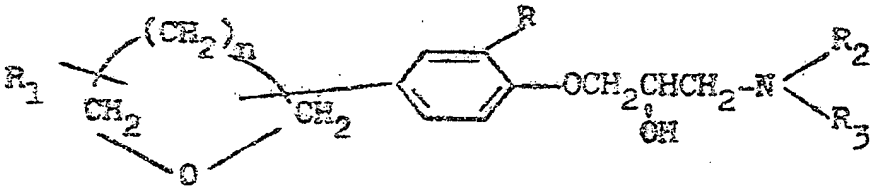
m is equal to zero, one, two or three.

The term lower alkyl denotes a radical having 1 to 4 carbon atoms.

The invention also embraces the pharmaceutically acceptable salts of these derivatives, such as the hydrochloride, oxalate, malonate, succinate and the like.

The new compounds according to the invention possess valuable pharmacological activities and can be used in therapy as a β-adrenergic cardioselective blocking agent.

Particularly interesting compounds are those of the formulae:



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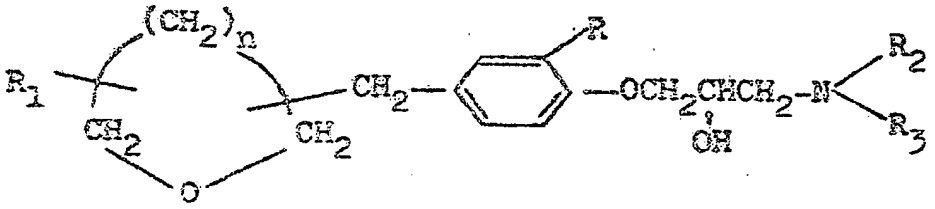


Ib

in which:

R_1 represents a hydrogen atom or the methyl or cyclopropyl radical,

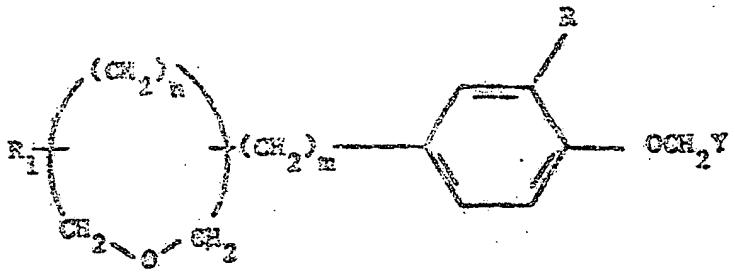
R_2 represents the isopropyl, t-butyl, dimethoxyphenylethyl or phenylisopropyl radical,

R_3 is a hydrogen atom,

R represents a hydrogen or halogen atom or the n-propyl, allyl or methoxy radical, and

n is equal to 2 or 3.

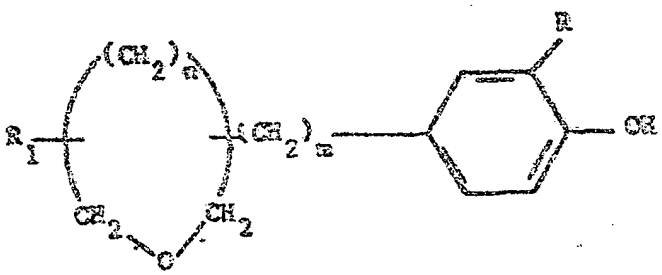
According to the invention, the compounds of the formula I can be prepared by the action of a compound of the formula II on an amine HNR_2R_3 in a customary organic solvent, especially the alcohols, or without a solvent, at a temperature of between 20 and 150°C; the desired product is isolated and optionally converted into a non-toxic acid addition salt in a manner which is in itself known:



II

In the formula II, R, R_1, n and m are defined as above, and Y can be a $-CH-CH_2$ (epoxy) group or a $-CHOH-CH_2X$ group, X in that case being a halogen atom. These compounds II are new.

In general terms, the compounds of the formula II can be obtained by reaction of a phenol of the formula III with an epihalogenohydrin, for example epichlorohydrin or epibromohydrin:



III

These compounds III are new.

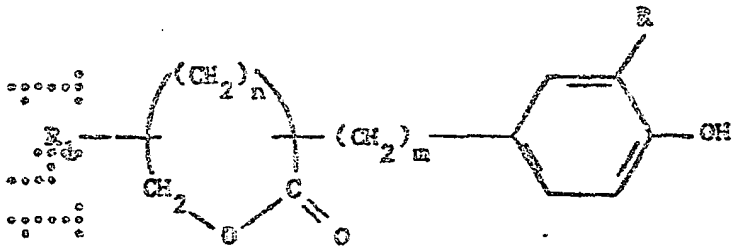
They can be isolated or obtained in a reaction mixture and, in the latter case, they can be used in the crude state without any purification.

The compounds of the formula II in which Y is the $-CH-CH_2$ (epoxy) group can be prepared by the action of epichlorohydrin or of epibromohydrin on a phenol of the formula III, which has beforehand been metallated by the usual metallation

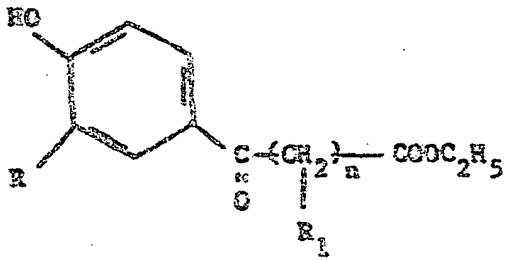
agents such as sodium hydroxide, potassium hydroxide, the methylates, the ethylates and the like, in an aqueous-alcoholic medium at a temperature of between 20 and 150°C.

The compounds of the formula II in which Y is the $-CHOH-CH_2X$ group can be prepared by the action of excess epichlorohydrin or epibromohydrin on a phenol of the formula III in the presence of a few drops of an amine catalyst such as piperidine, for example at a temperature of between 20 and 150°C, optionally 95-100°C.

The phenols of the formula III can be prepared by the action of a reducing agent such as the double hydride of aluminium and lithium, in an organic solvent such as tetrahydrofurane or ether, on a butyrolactone of the formula IV or on a keto-ester of the formula IV'

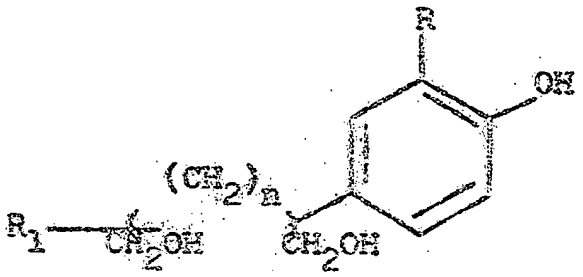


IV



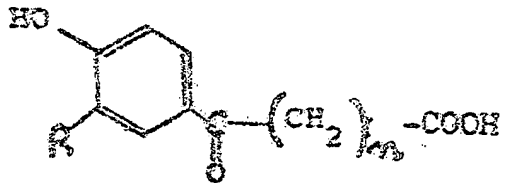
IV'

The phenols of the formula (III) can also be prepared by the action of a dehydrating agent such as, for example, para-toluenesulphonic acid, in an organic solvent such as benzene, toluene, xylene and the like, on diols of the formula (V).

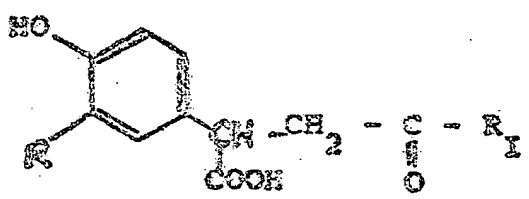


V

The butyrolactones of the formula IV can be prepared by reduction of the keto-acids of the formula (VI) and (VI') by means of a reducing agent such as, for example, sodium borohydride or potassium borohydride, in an aqueous-alcoholic basic medium.

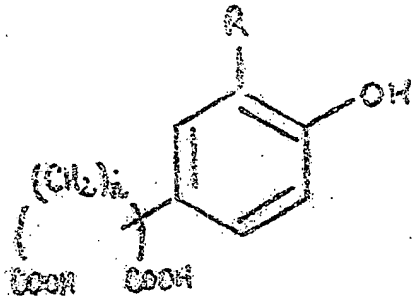


VI



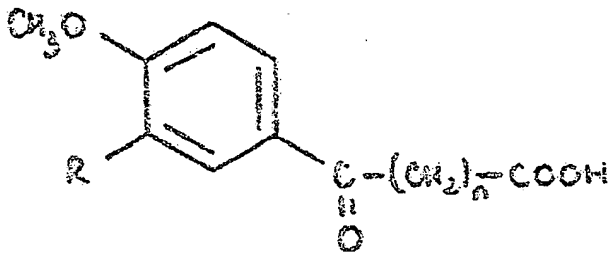
VI'

The diols of the formula (V) can be prepared by reduction of the keto-acids of the formulae (VI) and (VI') or of their esters, or of the diacids of the formula (VII) or of their diesters, by means of a reducing agent such as the double hydride of aluminium and lithium in an organic solvent such as tetrahydrofurane or ether.



VII

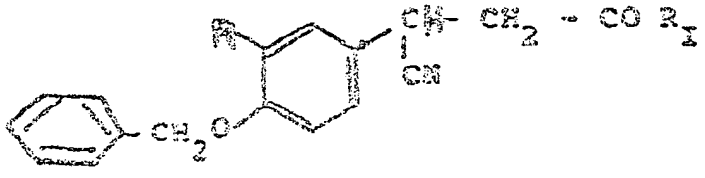
The keto-acid derivatives of the formula (VI) can be prepared by demethylation, by means of hydrobromic acid or pyridine hydrochloride, of derivatives of the formula (VIII)



VIII

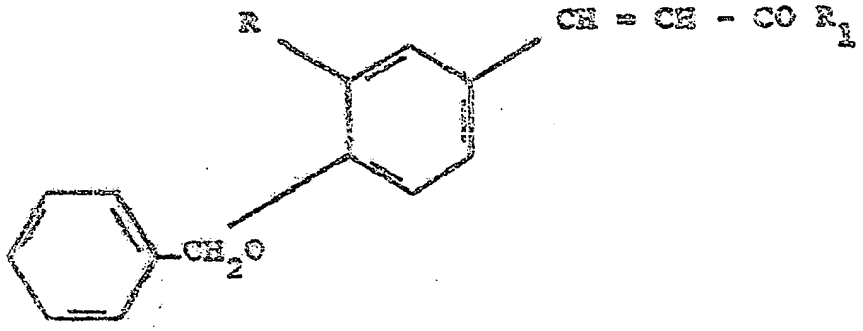
which can themselves be prepared by a conventional Friedel-Crafts reaction between a suitably substituted phenyl nucleus and succinic anhydride (n = 2) or glutaric anhydride (n = 3).

The keto-acid derivatives of the formula (VI') or the diacids of the formula (VII) in which n = 2 can be prepared by hydrolysis of the nitriles of the formula (IX)



IX

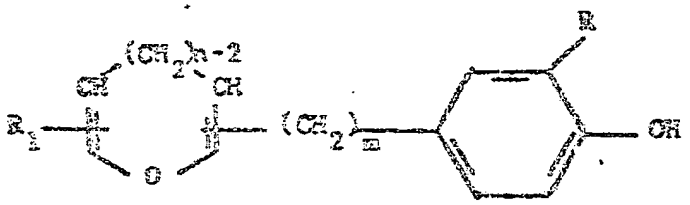
which are themselves obtained by an addition reaction of an alkali metal cyanide with the ethylenic derivatives of the formula (X)



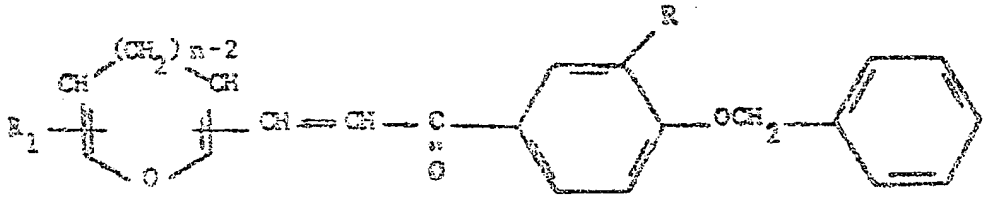
X

The liberation of the phenol can be carried out, and is in certain cases carried out, by debenzylation by means of catalytic hydrogenation of the benzylated phenol.

The phenols of the formula III can also be prepared by catalytic hydrogenation of phenols of the formula XI or of benzylphenols of the formula XII

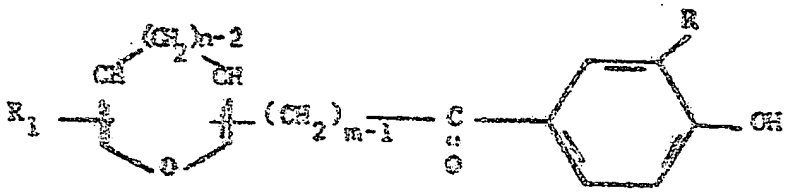


XI



XII

The phenols of the formula XI are prepared by reduction of the keto-phenols of the formula XIII

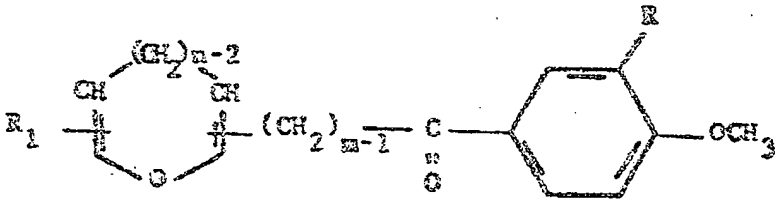


XIII

by means of sodium borchydride or potassium borohydride in a basic medium.

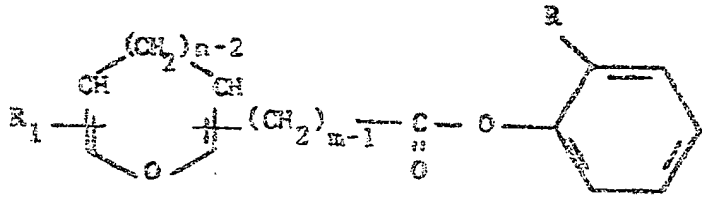
The benzylphenols of the formula XII are prepared by a conventional condensation reaction between a suitably substituted aldehyde and a suitably substituted acetophenone in a basic medium.

The keto-phenols of the formula XIII are prepared either by demethylation of the compounds of the formula XIV by means of pyridine hydrochloride



XIV

or by the conventional Fries reaction carried out on an ester of the formula XV



XV

In the formulae XIII, XIV and XV, m is at least equal to 1. The compounds of the formula XIV are themselves prepared by a Friedel-Crafts reaction on a suitably substituted methoxybenzene.

A substituent R = allyl can be introduced by a conventional Claisen rearrangement carried out on the phenol of the formula III, in which R = H, which has beforehand been allylated by means of an allyl halide in a basic medium.

A substituent R = $COCH_3$ can be introduced by a Fries rearrangement carried out on the phenol of the formula III, in which R = H, which has beforehand been acetylated.

If the starting phenol of the formula III does not contain halogen (R = H) a halogen can be introduced by the action of a halogen or a N-halogenosuccinimide on the said phenol.

The invention is illustrated by the non-limiting examples which follow, marked "*", the other examples illustrating preparation of intermediate compounds.

EXAMPLE 1

3-(4-HYDROXY-3-CHLORO-BENZOYL)-PROPIONIC ACID

FORMULA (VI), R = Cl, n = 2

A solution of 515 g of 3-(4-methoxy-3-chloro-benzoyl)-propionic acid, prepared by a Friedel-Crafts reaction of succinic anhydride with ortho-chloroanisole, and of 850 cm^3 of 66% strength hydrobromic acid in 850 cm^3 of acetic acid is heated under reflux for 12 hours.

The reaction mixture is then cooled and the crystals formed are filtered off, carefully washed with water and dried.

350 g of 3-(4-hydroxy-3-chloro-benzoyl)-propionic acid

are thus obtained in the form of crystals of melting point 159°C.

EXAMPLE 2

5-(4-HYDROXY-3-CHLORO-PHENYL)-BUTYROLACTONE

FORMULA (IV), R_1 = H, R = Cl, n = 2, m = 0

50 g of potassium borohydride are added to a solution of 100 g of 3-(4-hydroxy-3-chloro-benzoyl)-propionic acid, obtained in Example 1, and of 50 g of sodium hydroxide pellets in 200 cm^3 of distilled water and 500 cm^3 of methanol. After the end of the addition, the mixture is heated under reflux for 2 hours.

The cooled reaction mixture is then poured onto ice and hydrochloric acid. After standing overnight, the crystals formed are filtered off and then carefully washed with water and dried. 85 g of 5-(4-hydroxy-3-chloro-phenyl)-butyrolactone are thus obtained in the form of crystals of melting point 142-145°C.

EXAMPLE 3

2-(4-HYDROXY-3-CHLORO-PHENYL)-TETRAHYDROFURANE

FORMULA (III), R_1 = H, R = Cl, n = 2, m = 0

42.5 g of 5-(4-hydroxy-3-chloro-phenyl)-butyrolactone obtained in Example 2, dissolved in 200 cm^3 of tetrahydrofurane, are added dropwise to a suspension of 7.6 g of the double hydride of aluminium and lithium in 200 cm^3 of tetrahydrofurane.

The reaction mixture is then stirred for 4 hours at ambient temperature. After cooling the reaction (sic), a saturated aqueous solution of sodium sulphate is carefully

added dropwise. When the double hydride no longer reacts, the mixture is poured onto ice and hydrochloric acid, the organic products are then extracted with ether and the extract is washed with water and dried. After evaporation of the ether, the residue obtained, weighing 36 g, is filtered over silica gel; by elution with methylene chloride, 26 g of 2-(4-hydroxy-3-chloro-phenyl)-tetrahydrofurane are obtained in the form of white crystals of melting point 65°C.

EXAMPLE 4

1-[o-CHLORO-p-(TETRAHYDROFURANYL-2')]-PHENOXY-3-CHLORO-PROPAN-2-OL

FORMULA (II), R_1 = H, R = Cl, Y = CHOH-CH_2-Cl, n = 2, m = 0

A mixture of 10 g of 2-(4-hydroxy-3-chloro-phenyl)-tetrahydrofurane obtained in Example 3, 30 cm^3 of epichlorohydrin and 6 drops of piperidine is heated at 95-100°C for 6 hours.

The reaction mixture is then concentrated in vacuo and the oily residue obtained, which contains the desired product, is used in the crude form for the subsequent operations.

EXAMPLE 5 *

1-[o-CHLORO-p-(TETRAHYDROFURANYL-2')]-PHENOXY-3-ISOPROPYL-AMINO-PROPAN-2-OL

FORMULA (I), R_1 = H, R = Cl, R_2 = isopropyl, R_3 = H, n = 2, m = 0

A solution of 13.9 g of 1-[o-chloro-p-(tetrahydrofuranyl-2')]-phenoxy-3-chloro-propan-2-ol (obtained in Example 4) and of 30 cm^3 of isopropylamine in 30 cm^3 of methanol is

heated for 12 hours at 120°C in a sealed tube.

The reaction mixture is then concentrated in vacuo, after which it is taken up in 10% strength hydrochloric acid.

The neutral products are extracted 3 times with ether.

The aqueous phase is then cooled to 0°C and rendered alkaline, in the cold, by means of a 10% strength aqueous sodium hydroxide solution. The aminoalcohol is extracted with chloroform and the extract is washed with water, dried over sodium carbonate and decolorised with active charcoal.

After filtering, and evaporating the solvent, the residue obtained, which crystallises, is filtered off and then recrystallised from isopropyl ether.

6 g of 1-[o-chloro-p-(tetrahydrofuranyl-2')]-phenoxy-3-isopropylamino-propan-2-ol are thus obtained in the form of white crystals melting at 68-69°C.

EXAMPLE 6

2-(p-BENZYLOXYPHENYL)-BUTANE-1,4-DIOL

The benzyl derivative of the compound of the formula V, where R_1 = R = H and n = 2.

178 g of 2-(p-benzyloxyphenyl)-succinic acid are added, a little at a time, by means of a spatula, to a suspension of 40 g of the double hydride of aluminium and lithium in one litre of tetrahydrofurane, with good stirring.

After the end of the addition, the mixture is stirred for a further 6 hours at ambient temperature. It is then cooled to 0°C and a saturated aqueous sodium sulphate solution is added carefully. When the double hydride of aluminium

and lithium no longer reacts, the mixture is filtered. The filtrate is concentrated in vacuo and the residue is taken up in petroleum ether. The crystals formed are filtered off. 96 g of 2-(p-benzyloxyphenyl)-butane-1,4-diol are thus obtained in the form of white crystals of melting point 96-98°C.

EXAMPLE 7

3-(p-BENZYLOXYPHENYL)-TETRAHYDROFURANE

The benzyl derivative of the compound of the formula III, where $R_1 = R = H$, $n = 2$ and $m = 0$

A solution of 95 g of 2-(p-benzyloxyphenyl)-butane-1,4-diol obtained in Example 6 and 20 g of para-toluenesulphonic acid in 300 cm^3 of toluene is heated under reflux for 2 hours, using a water separator.

The reaction mixture is then cooled, after which it is washed with water, a 5% strength sodium hydroxide solution and again with water. After drying over sodium sulphate, the organic phase is freed from the solvent by evaporation and the residue obtained, weighing 75 g, is filtered over silica gel, the eluant being benzene. 59 g of 3-(p-benzyloxyphenyl)-tetrahydrofurane are thus obtained in the form of white crystals of melting point below 50°C.

EXAMPLE 8

3-(p-HYDROXYPHENYL)-TETRAHYDROFURANE

FORMULA III, $R_1 = R = H$, $n = 2$, $m = 0$

A solution of 59 g of 3-(p-benzyloxyphenyl)-tetrahydrofurane obtained in Example 7, in 300 cm^3 of methylcellosolve containing 4 g of 5% strength Pd/C is subjected to

hydrogenation under normal pressure and at ambient temperature.

After the theoretical amount of hydrogen has been absorbed, the catalyst is filtered off and the mother liquors are evaporated in vacuo. The crystals obtained are recrystallised from toluene. 22.4 g of 3-(p-hydroxyphenyl)-tetrahydrofurane are thus isolated in the form of white crystals of melting point 97-99°C.

EXAMPLE 9

3-[p-(TETRAHYDROFURANYL-3')]-PHENOXY-1,2-EPOXY-PROPANE

FORMULA II, R_1 = R = H, Y - $\underset{O}{\overset{CH}{\diagdown\diagup}}-CH_2$, n = 2, m = 0

A solution of 9 g of 3-(p-hydroxyphenyl)-tetrahydrofurane obtained in Example 8, 3.7 g of potassium hydroxide dissolved in 40 cm^3 of water and 10 cm^3 of epichlorohydrin in 250 cm^3 of ethanol is stirred for 24 hours at ambient temperature.

The reaction mixture is then concentrated in vacuo, the residue is then taken up in chloroform and the solution is washed with water, with a 5% strength sodium hydroxide solution and again with water. After having dried the chloroform phase, the solvent is evaporated and 11.9 g of 3-[p-(tetrahydrofuranyl-3')]-phenoxy-1,2-epoxy-propane are obtained in the form of an oil which is used in the crude form for the next stage.

EXAMPLE 10 *

1-[p-(TETRAHYDROFURANYL-3')]-PHENOXY-3-ISOPROPYLAMINO-PROPAN-2-OL

FORMULA (I), R_1 = R = H, R_2 = isopropyl, R_3 = H, n = 2, m = 0

A solution of 11.9 g of 3-[p-(tetrahydrofuranyl-3')]-

phenoxy-1,2-epoxy-propane obtained in Example 9 and of 30 cm^3 of isopropylamine in 40 cm^3 of isopropanol is heated for 7 hours at 120-130°C in a sealed tube. The reaction mixture is then concentrated in vacuo, after which it is taken up in 10% strength hydrochloric acid. The neutral products are extracted 3 times with ether.

The aqueous phase is then cooled to 0°C and rendered alkaline, in the cold, by means of a 10% strength aqueous sodium hydroxide solution. The aminoalcohol is extracted with chloroform and the extract is washed with water, dried over sodium carbonate and decolorised by means of active charcoal. After filtering, and evaporating the solvent, the oily residue obtained crystallises on trituration in a mixture of pentane and ether. By recrystallising the crystals obtained from cyclohexane, 7 g of 1-[p-(tetrahydrofuranyl-3')]-phenoxy-3-isopropylamino-propan-2-ol are isolated in the form of white crystals of melting point 48-49°C.

EXAMPLE 11

3-[o-CHLORO-p-(TETRAHYDROFURANYL-2')]-PHENOXY-1,2-EPOXY-PROPANE

FORMULA II, R_1 = H, R = Cl, Y = $-CH\underset{O}{\diagdown\diagup}CH_2$, n = 2, m = 0

The procedure of Example 9 is followed, but using 29 g of 2-(4'-hydroxy-3'-chloro-phenyl)-tetrahydrofurane obtained in Example 3. 35 g of 3-[o-chloro-p-(tetrahydrofuranyl-2')]-phenoxy-1,2-epoxy-propane are recovered in the form of an oil which is used, in the crude form, for the next stage.

EXAMPLE 12 *

HYDROCHLORIDE OF 1-[o-CHLORO-p-(TETRAHYDROFURANYL-2')]-PHENOXY-3-TERT.-BUTYLAMINO-PROPAN-2-OL

FORMULA (I), R_1 = H, R = Cl, R_2 = tert.-butyl, R_3 = H, n = 2

A solution of 12 g of 3-[o-chloro-p-(tetrahydrofuranyl-2')]-phenoxy-1,2-epoxy-propane obtained in Example 11 and of 30 cm^3 of tert.-butylamine in 40 cm^3 of isopropanol is heated at 120-130°C in a sealed tube for 7 hours.

The reaction mixture is then concentrated in vacuo, the residue is taken up in 10% strength hydrochloric acid so as to obtain an acid pH, and the neutral products are extracted 3 times with ether.

The hydrochloride is then extracted from the mother liquors by three extractions with chloroform.

The chloroform phase is dried over sodium sulphate and the chloroform is evaporated in vacuo. The residue obtained is taken up in ether and the crystals formed are filtered off. After recrystallisation from acetone, 6.5 g of the hydrochlorides of 1-[o-chloro-p-(tetrahydrofuranyl-2')]-phenoxy-3-tert.-butylamino-propan-2-ol are obtained in the form of white crystals of melting point 147-148°C.

EXAMPLE 13 *

HYDROCHLORIDE OF 1-[o-CHLORO-p-(TETRAHYDROFURANYL-2')]-PHENOXY-3-(3",4"-DIMETHOXYPHENYL)-ETHYLAMINO-PROPAN-2-OL

FORMULA I, R_1 = H, R = Cl, R_2 = CH_3  R_3 = H, n = 2, m = 0

The procedure of Example 12 is followed, but starting from 12 g of 3-[o-chloro-p-[tetrahydrofuranyl-2')]-phenoxy-1,2-epoxy-propane obtained in Example 11 and 10 g of homo-veratrylamine. 8 g of the hydrochloride of 1-[o-chloro-p-(tetrahydrofuranyl-2')]-phenoxy-3-(3",4"-dimethoxyphenyl)-ethylamino-propan-2-ol are obtained in the form of white crystals of melting point 130-133°C.

EXAMPLE 14

2-(p-HYDROXYPHENYL)-TETRAHYDROFURANE

FORMULA III, $R_1 = R = H$, $n = 2$, $m = 0$

A solution of 216 g of the ethyl ester of 3-p-hydroxy-benzoyl-propionic acid in 1 litre of tetrahydrofurane is added dropwise to a suspension of 55 g of the double hydride of aluminium and lithium in 1 litre of tetrahydrofurane, the exothermic reaction being left to develop and being controlled by the dropwise addition.

The addition lasts 1 hour 30 minutes, after which the mixture is left, whilst being stirred, for 3 hours, and is then left to stand overnight.

After cooling the reaction mixture, a little ethyl acetate is added, followed by careful addition of a saturated aqueous sodium sulphate solution. When the hydride no longer reacts, the mixture is poured onto ice and hydrochloric acid, the organic products are then extracted with methylene chloride, and the extract is dried and evaporated. After recrystallising the residue obtained from toluene, 120 g of 2-(p-hydroxyphenyl)-tetrahydrofurane are recovered in the form of white crystals of melting point 110°C.

EXAMPLE 15

3-[p-(TETRAHYDROFURANYL-2')]-PHENOXY-1,2-EPOXY-PROPANE

FORMULA II, $R_1 = R = H$, $Y = -CH\underset{O}{\diagdown\diagup}CH_2$, $n = 2$

The procedure of Example 9 is followed, but using 12 g of 2-(p-hydroxyphenyl)-tetrahydrofurane obtained in Example 14. 16 g of 3-[p-(tetrahydrofuranyl-2')]-phenoxy-1,2-epoxy-propane are recovered in the form of an oil which is used in the crude form for the next stage.

EXAMPLE 16 *

1-[p-(TETRAHYDROFURANYL-2')]-PHENOXY-3-ISOPROPYLAMINO-PROPAN-2-OL

FORMULA I, $R_1 = R = H$, R_2 = isopropyl, $R_3 = H$, $n = 2, m = 0$

The procedure of Example 5 is followed, but using 14 g of 3-[p-(tetrahydrofuranyl-2')]-phenoxy-1,2-epoxy-propane obtained in Example 15. After recrystallisation from petroleum ether, 10 g of 1-[p-(tetrahydrofuranyl-2')]-phenoxy-3-isopropylamino-propan-2-ol are recovered in the form of white crystals of melting point 57-58°C. In order to prepare the hydrochloride of this base, the latter is dissolved in acetone and is neutralised by adding a solution of hydrochloric acid in ether; the crystals formed are filtered off and washed with ether. The hydrochloride is thus recovered in the form of white crystals of melting point 112-115°C.

EXAMPLE 17 *

1-[p-(TETRAHYDROFURANYL-2')]-PHENOXY-3-TERT.-BUTYLAMINO-PROPAN-2-OL

FORMULA I, $R_1 = R = H$, R_2 = tert.-butyl, $R_3 = H$, $n = 2, m = 0$

The procedure of Example 5 is followed, but using 16 g of 3-[p-(tetrahydrofuranyl-2')]-phenoxy-1,2-epoxy-propane obtained in Example 15 and 30 cm^3 of tert.-butyl-amine. After recrystallisation from a mixture of petroleum ether and ether, 12 g of 1-[p-(tetrahydrofuranyl-2')]-phenoxy-3-tert.-butylamino-propan-2-ol are recovered in the form of white crystals of melting point 69-71°C.

EXAMPLE 18

2-(4-HYDROXY-3-ALLYL-PHENYL)-TETRAHYDROFURANE

FORMULA III, R_1 = H, R = allyl, n = 2, m = 0

49.2 g of 2-(p-hydroxyphenyl)-tetrahydrofurane obtained in Example 14 are metallated by means of sodium methylate obtained from 7.6 g of sodium in 300 cm^3 of methanol. 43.5 g of allyl bromide are then added to this solution, after which the mixture is heated under reflux for 3 hours. The reaction mixture is then concentrated in vacuo, water is added and the mixture is extracted with ether. The extract is washed with a 5% strength sodium hydroxide solution and then with water and is dried over sodium sulphate. After evaporating the solvent, the residue obtained (57 g) is dissolved in 300 cm^3 of diphenyl ether and the solution is heated under reflux for 1 hour 30 minutes. The reaction mixture is then cooled and the phenol is extracted with a 10% strength potassium hydroxide solution. The alkaline phase is extracted with ether and then acidified in the cold with 10% strength hydrochloric acid. The phenol is then extracted with chloroform and the extract is washed with water and dried over sodium sulphate. After evapora-

ting the solvent, the residue obtained (46 g) is filtered over a little silica gel, the eluant being benzene. 36 g of 2-(4-hydroxy-3-allyl-phenyl)-tetrahydrofurane are thus recovered in the form of a colourless oil.

EXAMPLE 19

3-[o-ALLYL-p-(TETRAHYDROFURANYL-2')]-PHENOXY-1,2-EPOXY-PROPANE

FORMULA II, R_1 = H, R = allyl, Y = $-CH-CH_2$ (O), n = 2, m = 0

The procedure of Example 9 is followed, but using 24 g of 2-(4-hydroxy-3-allyl-phenyl)-tetrahydrofurane obtained in Example 18; 28 g of 3-[o-allyl-p-(tetrahydrofuranyl-2')]-phenoxy-1,2-epoxy-propane are recovered in the form of an oil, which is used, in the crude form, for the next stage.

EXAMPLE 20 *

HYDROCHLORIDE OF 1-[o-ALLYL-p-(TETRAHYDROFURANYL-2')]-PHENOXY-3-ISOPROPYLAMINO-PROPAN-2-OL

FORMULA I, R_1 = H, R = allyl, R_2 = isopropyl, R_3 = H, n = 2, m = 0

The procedure of Example 12 is followed, but using 14 g of 3-[o-allyl-p-(tetrahydrofuranyl-2')]-phenoxy-1,2-epoxy-propane obtained in Example 19 and 30 cm^3 of isopropyl-amine. After recrystallisation from ethyl acetate, 9.1 g of the hydrochloride of 1-[o-allyl-p-(tetrahydrofuranyl-2')]-phenoxy-3-isopropylamino-propan-2-ol are obtained in the form of white crystals of melting point 102-104°C.

EXAMPLE 21 *

HYDROCHLORIDE OF 1-[o-ALLYL-p-(TETRAHYDROFURANYL-2')]-PHENOXY-3-TERT.-BUTYLAMINO-PROPAN-2-OL

FORMULA I, R_1 = H, R = allyl, R_2 = tert.-butyl, R_3 = H, n = 2, m = 0

The procedure of Example 12 is followed, but using 14 g of 3-[o-allyl-p-(tetrahydrofuranyl-2')]-phenoxy-1,2-epoxy-propane obtained in Example 19 and 30 cm^3 of tert.-butylamine. After recrystallisation from a mixture of acetone and ether, 10.8 g of the hydrochloride of 1-[o-allyl-p-(tetrahydrofuranyl-2')]-phenoxy-3-tert.-butylamino-propan-2-ol are obtained in the form of white crystals of melting point 103-105°C.

EXAMPLE 22

2-(4-HYDROXY-3-BROMO-PHENYL)-TETRAHYDROFURANE

FORMULA III, R_1 = H, R = Br, n = 2

A solution of 33 g of N-bromosuccinimide in 100 cm^3 of dimethylformamide is added dropwise to a solution of 31 g of 2-(p-hydroxyphenyl)-tetrahydrofurane, obtained in Example 14, in 100 cm^3 of dimethylformamide, whilst cooling with a mixture of water and ice. The product is allowed to return to ambient temperature and is then stirred for 5 hours.

After the reaction mixture has stood overnight, water is added to it and the organic products are extracted with ether. The phenol is extracted from the ether phase by means of a 10% strength aqueous sodium hydroxide solution. The alkaline phase is acidified in the cold by means of 10% strength hydrochloric acid and the phenol is extracted with ether, the extract being washed with water and dried over sodium sulphate. After evaporating the solvent, the residue crystallises from pentane. After recrystallisa-

tion from a mixture of heptane and ether, 34 g of 2-(4-hydroxy-3-bromo-phenyl)-tetrahydrofurane are recovered in the form of white crystals of melting point 67-69°C.

EXAMPLE 23

3-[o-BROMO-p-(TETRAHYDROFURANYL-2')]-PHENOXY-1,2-EPOXY-PROPANE

FORMULA II, R_1 = H, R = Br, Y = $-CH-CH_2$ (O), n = 2, m = 0

The procedure of Example 9 is followed, but using 12 g of 2-(4-hydroxy-3-bromo-phenyl)-tetrahydrofurane obtained in Example 22; 14.5 g of 3-[o-bromo-p-(tetrahydrofuranyl-2')]-phenoxy-1,2-epoxy-propane are recovered in the form of an oil which is used in the crude form for the next stage.

EXAMPLE 24 *

1-[o-BROMO-p-(TETRAHYDROFURANYL-2')]-PHENOXY-3-ISOPROPYL-AMINO-PROPAN-2-OL

FORMULA I, R_1 = H, R = Br, R_2 = isopropyl, R_3 = H, n = 2

The procedure of Example 5 is followed, but using 8 g of 3-[o-bromo-p-(tetrahydrofuranyl-2')]-phenoxy-1,2-epoxy-propane obtained in Example 23 and 20 cm^3 of isopropyl-amine. After recrystallisation from isopropyl ether, 5.3 g of 1-[o-bromo-p-(tetrahydrofuranyl-2')]-phenoxy-3-isopropylamino-propan-2-ol are recovered in the form of white crystals of melting point 75-77°C.

EXAMPLE 25 *

HYDROCHLORIDE OF 1-[o-BROMO-p-(TETRAHYDROFURANYL-2')]-PHENOXY-3-TERT.-BUTYLAMINO-PROPAN-2-OL

FORMULA I, R_1 = H, R = Br, R_2 = tert.-butyl, R_3 = H, n = 2, m = 0

The procedure of Example 12 is followed, but using 14.5 g of 3-[o-bromo-p-(tetrahydrofuranyl-2')]-phenoxy-1,2-epoxy-propane obtained in Example 23 and 30 cm^3 of tert.-butylamine. After recrystallisation from a mixture of acetone and ether, 12 g of the hydrochloride of 1-[o-bromo-p-(tetrahydrofuranyl-2')]-phenoxy-3-tert.-butylamino-propan-2-ol are obtained in the form of white crystals of melting point 142-144°C.

EXAMPLE 26 *

HYDROCHLORIDE OF 1-[o-BROMO-p-(TETRAHYDROFURANYL-2')]-PHENOXY-3-(3",4"-DIMETHOXYPHENYL)-ETHYLAMINO-PROPAN-2-OL

FORMULA I, R_1 = H, R = Br, n = 2

R_2 =  CH_2-CH_2- , R_3 = H

The procedure of Example 12 is followed, but using 14 g of 3-[o-bromo-p-(tetrahydrofuranyl-2')]-phenoxy-1,2-epoxy-propane obtained in Example 23 and 10 g of homoveratrylamine. After recrystallisation from a mixture of acetone and ether, 6.2 g of the hydrochloride of 1-[o-bromo-p-(tetrahydrofuranyl-2')]-phenoxy-3-(3",4"-dimethoxyphenyl)-ethylamino-propan-2-ol are obtained in the form of white crystals of melting point 116-120°C.

EXAMPLE 27 *

HYDROCHLORIDE OF 1-[o-BROMO-p-(TETRAHYDROFURANYL-2')]-PHENOXY-3-(3-PHENYL-ISOPROPYLAMINO)-PROPAN-2-OL

FORMULA I, R_1 = H, R = Br, n = 2, m= 0

R_2 =  CH_2-CH- , R_3 = H
CH_3

The procedure of Example 12 is followed, but using

13 g of 3-[o-bromo-p-(tetrahydrofuranyl-2')]-phenoxy-1,2-epoxy-propane obtained in Example 23 and 6.5 g of dexamphetamine. After recrystallisation from a mixture of acetone and ether, 2.9 g of the hydrochloride of 1-[o-bromo-p-(tetrahydrofuranyl-2')]-phenoxy-3-(β-phenyl-isopropylamino)-propan-2-ol are obtained in the form of white crystals of melting point 132-138°C.

EXAMPLE 28

3-(4-HYDROXY-3-ALLYL-PHENYL)-TETRAHYDROFURANE

FORMULA III, R_1 = H, R = allyl, n = 2, m = 0

The procedure of Example 18 is followed, but starting from 11.4 g of 3-(p-hydroxyphenyl)-tetrahydrofurane obtained in Example 8. 8 g of 3-(4-hydroxy-3-allyl-phenyl)-tetrahydrofurane are obtained in the form of white crystals of melting point 50-52°C.

EXAMPLE 29

3-[o-ALLYL-p-(TETRAHYDROFURANYL-3')]-PHENOXY-1,2-EPOXY-PROPANE

FORMULA II, R_1 = H, R = allyl, Y = $-CH-CH_2$ (with O), n = 2, m = 0

The procedure of Example 9 is followed, but using 8 g of 3-(4-hydroxy-3-allyl-phenyl)-tetrahydrofurane obtained in Example 28. 9 g of 3-[o-allyl-p-(tetrahydrofuranyl-3')]-phenoxy-1,2-epoxy-propane are recovered in the form of an oil, which is used, in the crude form, for the next stage.

EXAMPLE 30 *

HYDROCHLORIDE OF 1-[o-ALLYL-p-(TETRAHYDROFURANYL-3')]-PHENOXY-3-ISOPROPYLAMINO-PROPAN-2-OL

FORMULA I, R_1 = H, R = allyl, R_2 = isopropyl, R_3 = H,

n = 2, m = 0

The procedure of Example 12 is followed, but using 9 g of 3-[o-allyl-p-(tetrahydrofuranyl-3')]-phenoxy-1,2-epoxy-propane obtained in Example 29 and 30 cm^3 of isopropylamine. After recrystallisation from ethyl acetate, 4.5 g of the hydrochloride of 1-[o-allyl-p-(tetrahydrofuranyl-3')]-phenoxy-3-isopropylamino-propan-2-ol are obtained in the form of white crystals of melting point 91-3°C.

EXAMPLE 31

2-(4-BENZYLOXY-3-METHOXY-PHENYL)-BUTANE-1,4-DIOL

The benzyl derivative of the compound of the formula V, where R_1 = H, R = OCH_3 and n = 2.

The procedure of Example 6 is followed, but starting from 144 g of 2-(4-benzyloxy-3-methoxy-phenyl)-succinic acid. 105 g of 2-(4-benzyloxy-3-methoxy-phenyl)-butane-1,4-diol are obtained in the form of a thick oil, which is used, in the crude form, for the subsequent operations.

EXAMPLE 32

3-(4-BENZYLOXY-3-METHOXY-PHENYL)-TETRAHYDROFURANE

The benzyl derivative of the compound of the formula III, where R_1 = H, R = OCH_3, n = 2 and m = 0

The procedure of Example 7 is followed, but using 105 g of 2-(4-benzyloxy-3-methoxy-phenyl)-butane-1,4-diol obtained in Example 31. 83 g of 3-(4-benzyloxy-3-methoxy-phenyl)-tetrahydrofurane are recovered in the form of an oil, which is used, in the crude form, for the subsequent operations.

EXAMPLE 33

3-(4-HYDROXY-3-METHOXY-PHENYL)-TETRAHYDROFURANE

FORMULA III, R_1 = H, R = OCH_3, n = 2, m = 0

The procedure of Example 8 is followed, but using 83 g of 3-(4-benzyloxy-3-methoxy-phenyl)-tetrahydrofurane obtained in Example 32. After filtration over silica gel, the eluant being methylene chloride, 31 g of 3-(4-hydroxy-3-methoxy-phenyl)-tetrahydrofurane are recovered in the form of white crystals of melting point 65-68°C.

EXAMPLE 34

3-[o-METHOXY-p-(TETRAHYDROFURANYL-3')]-PHENOXY-1,2-EPOXY-PROPANE

FORMULA II, R_1 = H, R = OCH_3, Y = $-CH\overset{O}{<}CH_2$, n = 2, m = 0

The procedure of Example 9 is followed, but using 19.7 g of 3-(4-hydroxy-3-methoxy-phenyl)-tetrahydrofurane obtained in Example 33. 25 g of 3-[o-methoxy-p-(tetrahydrofuranyl-3')]-phenoxy-1,2-epoxy-propane are recovered in the form of an oil, which is used, in the crude form, for the subsequent operations.

EXAMPLE 35 *

1-[o-METHOXY-p-(TETRAHYDROFURANYL-3')]-PHENOXY-3-ISOPROPYL-AMINO-PROPAN-2-OL

FORMULA I, R_1 = H, R = OCH_3, R_2 = isopropyl, R_3 = H, n = 2, m = 0

The procedure of Example 5 is followed, but using 10 g of 3-[o-methoxy-p-(tetrahydrofuranyl-3')]-phenoxy-1,2-epoxy-propane obtained in Example 34 and 30 cm^3 of isopropyl-amine. After recrystallisation from isopropyl ether,

5.5 g of 1-[o-methoxy-p-(tetrahydrofuranyl-3')]-phenoxy-3-isopropylamino-propan-2-ol are recovered in the form of white crystals of melting point 53-54°C.

EXAMPLE 36 *

HYDROCHLORIDE OF 1-[o-METHOXY-p-(TETRAHYDROFURANYL-3')]-PHENOXY-3-TERT.-BUTYLAMINO-PROPAN-2-OL

FORMULA I, R_1 = H, R = OCH_3, R_2 = tert.-butyl, R_3 = H, n = 2, m = 0

The procedure of Example 12 is followed but using 10 g of 3-[o-methoxy-p-(tetrahydrofuranyl-3')]-phenoxy-1,2-epoxy-propane obtained in Example 34 and 30 cm^3 of tert.-butylamine. After recrystallisation from ethyl acetate, 4.3 g of the hydrochloride of 1-[o-methoxy-p-(tetrahydrofuranyl-3')]-phenoxy-3-tert.-butylamino-propan-2-ol are recovered in the form of white crystals of melting point 99-101°C.

EXAMPLE 37

2-(p-BENZYLOXYPHENYL)-3-CYANO-1-CYCLOPROPYL-PROPAN-1-ONE

FORMULA IX, R = H, R_1 = cyclopropyl

97.5 g of 3-(p-benzyloxyphenyl)-1-cyclopropyl-prop-2-en-1-one, obtained by a Claisen condensation of p-benzyloxy-benzaldehyde and methyl cyclopropyl ketone, are dissolved in 1.2 litres of methanol and 120 cm^3 of ethyl acetate by heating to near the reflux temperature. A solution of 60 g of sodium cyanide in 120 cm^3 of water is rapidly added dropwise to the above solution.

After the end of the addition, the reaction mixture is heated for 5 hours under reflux and is then concentrated

to half its volume and cooled, and 500 cm^3 of water are added slowly, with good stirring. The crystals obtained are filtered off and then thoroughly washed with water and dried. 90 g of 3-(p-benzyloxyphenyl)-3-cyano-1-cyclopropyl-propan-1-one are thus recovered in the form of light beige crystals of melting point 85-6°C.

EXAMPLE 38

3-(p-BENZYLOXYPHENYL)-3-CARBOXY-1-CYCLOPROPYL-PROPAN-1-ONE

FORMULA VI', R = H, R_1 = cyclopropyl

A solution of 85 g of 3-(p-benzyloxyphenyl)-3-cyano-1-cyclopropyl-propan-1-one obtained in Example 37, and 40 g of sodium hydroxide in 75 cm^3 of water and 750 cm^3 of ethanol is heated under reflux for 24 hours.

The reaction mixture is then cooled, after which it is poured into 2 litres of water and ice, and then extracted 3 times with ether. The mother liquors are acidified in the cold with 10% strength hydrochloric acid and the acid is extracted 3 times with ether; the extract is washed with water and dried over sodium sulphate. After evaporating the ether, 75.4 g of 3-(p-benzyloxyphenyl)-3-carboxy-1-cyclopropyl-propan-1-one are recovered in the form of white crystals of melting point 96°C.

EXAMPLE 39

3-(p-BENZYLOXYPHENYL)-1-CYCLOPROPYL-BUTANE-1,4-DIOL

The benzyl derivative of the compound of the formula V, where R = H, R_1 = cyclopropyl and n = 2.

The procedure of Example 6 is followed, but starting from 48.6 g of 3-(p-benzyloxyphenyl)-3-carboxy-1-cyclopropyl-

propan-1-one obtained in Example 38. 38 g of 3-(p-benzyloxyphenyl)-1-cyclopropyl-butane-1,4-diol are obtained in the form of white crystals of melting point 125°C.

EXAMPLE 40

4-(p-BENZYLOXYPHENYL)-2-CYCLOPROPYL-TETRAHYDROFURANE

The benzyl derivative of the compound of the formula III, where R_1 = cyclopropyl, R = H, n = 2 and m = 0

The procedure of Example 7 is followed, but using 38 g of 3-(p-benzyloxyphenyl)-1-cyclopropyl-butane-1,4-diol obtained in Example 39. After filtration over silica gel, the eluant being benzene, 29 g of 4-(p-benzyloxyphenyl)-2-cyclopropyl-tetrahydrofurane are recovered in the form of an oil.

EXAMPLE 41

4-(p-HYDROXYPHENYL)-2-CYCLOPROPYL-TETRAHYDROFURANE

FORMULA III, R_1 = cyclopropyl, R = H, n = 2, m = 0

The procedure of Example 8 is followed, but using 29 g of 4-(p-benzyloxyphenyl)-2-cyclopropyl-tetrahydrofurane obtained in Example 40. 19 g of 4-(p-hydroxyphenyl)-2-cyclopropyl-tetrahydrofurane are recovered in the form of white crystals of melting point 79-80°C.

EXAMPLE 42

1-[p-(2'-CYCLOPROPYL-TETRAHYDROFURANYL-4')]-PHENOXY-3-CHLORO-PROPAN-2-OL

FORMULA II, R_1 = cyclopropyl, R = H, Y = $CHOHCH_2Cl$, n = 2, m = 0

A mixture of 16.2 g of 4-(p-hydroxyphenyl)-2-cyclopropyl-tetrahydrofurane obtained in Example 41, 75 cm^3 of

epichlorohydrin and 6 drops of piperidine is heated at 95-100°C for 7 hours. The reaction mixture is then concentrated in vacuo and the residue is taken up in ether. The ether solution is washed in the cold with 50 cm^3 of 5% strength hydrochloric acid and then with 3 times 50 cm^3 of water. It is then dried, after which the ether is evaporated in vacuo. 22 g of 1-[p-(2'-cyclopropyl-tetrahydrofuranyl-4')]-phenoxy-3-chloro-propan-2-ol are thus isolated in the form of an oily residue which is used, in the crude form, for the subsequent operations.

EXAMPLE 43 *

HYDROCHLORIDE OF 1-[p-(2'-CYCLOPROPYL-TETRAHYDROFURANYL-4')]-PHENOXY-3-ISOPROPYLAMINO-PROPAN-2-OL

FORMULA I, R_1 = cyclopropyl, R = H, R_2 = isopropyl, R_3 = H, n = 2, m = 0

The procedure of Example 12 is followed, but using 11 g of 1-[p-(2'-cyclopropyl-tetrahydrofuranyl-4')]-phenoxy-3-chloro-propan-2-ol obtained in Example 42 and 40 cm^3 of isopropylamine. After recrystallisation from a mixture of acetone and ether, 8.3 g of the hydrochloride of 1-[p-(2'-cyclopropyl-tetrahydrofuranyl-4')]-phenoxy-3-isopropyl-amino-propan-2-ol are obtained in the form of white crystals of melting point 100°C.

EXAMPLE 44 *

HYDROCHLORIDE OF 1-[p-(2'-CYCLOPROPYL-TETRAHYDROFURANYL-4')]-PHENOXY-3-TERT.-BUTYLAMINO-PROPAN-2-OL

FORMULA I, R_1 = cyclopropyl, R = H, R_2 = tert.-butyl, R_3 = H, n = 2, m = 0

The procedure of Example 12 is followed, but using 11 g of 1-[p-(2'-cyclopropyl-tetrahydrofuranyl-4')]-phenoxy-3-chloro-propan-2-ol obtained in Example 42 and 40 cm^3 of tert.-butylamine. After recrystallisation from a mixture of acetone and ether, 9.7 g of the hydrochloride of 1-[p-(2'-cyclopropyl-tetrahydrofuranyl-4')]-phenoxy-3-tert.-butylamino-propan-2-ol are obtained in the form of white crystals of melting point 135°C.

EXAMPLE 45

3-(4-HYDROXY-3-BROMO-PHENYL)-TETRAHYDROFURANE

FORMULA III, R_1 = H, R = Br, n = 2, m = 0

The procedure of Example 22 is followed, but using 18.3 g of 3-(p-hydroxyphenyl)-tetrahydrofurane obtained in Example 8. After filtration over silica gel, the eluant being methylene chloride, 18 g of 3-(4-hydroxy-3-bromo-phenyl)-tetrahydrofurane are obtained in the form of a colourless oil.

EXAMPLE 46

3-[o-BROMO-p-(TETRAHYDROFURANYL-3')]-PHENOXY-1,2-EPOXY-PROPANE

FORMULA II, R_1 = H, R = Br, Y = $-CH-CH_2$ (with O), n = 2, m = 0

The procedure of Example 9 is followed, but using 18 g of 3-(4-hydroxy-3-bromo-phenyl)-tetrahydrofurane obtained in Example 45. 21.5 g of 3-[o-bromo-p-(tetrahydrofuranyl-3')]-phenoxy-1,2-epoxy-propane are recovered in the form of an oil, which, in the crude form, is used for the next stage.

EXAMPLE 47 *

HYDROCHLORIDE OF 1-[o-BROMO-p-(TETRAHYDROFURANYL-3')]-PHENOXY-3-ISOPROPYLAMINO-PROPAN-2-OL

FORMULA I, R_1 = H, R = Br, R_2 = isopropyl, R_3 = H, n = 2, m = 0

The procedure of Example 5 is followed, but using 11 g of 3-[o-bromo-p-(tetrahydrofuranyl-3')]-phenoxy-1,2-epoxy-propane obtained in Example 46 and 30 cm^3 of isopropylamine. 1-[o-Bromo-p-(tetrahydrofuranyl-3')]-phenoxy-3-isopropylamino-propan-2-ol is recovered*. To prepare the hydrochloride of this base, the latter is dissolved in acetone and neutralised by adding a solution of hydrogen chloride in ether. The crystals formed are filtered off and washed with ether. 7.2 g of hydrochloride are thus recovered in the form of white crystals of melting point 147-149°C.

EXAMPLE 48 *

HYDROCHLORIDE OF 1-[o-BROMO-p-(TETRAHYDROFURANYL-3')]-PHENOXY-3-TERT.-BUTYLAMINO-PROPAN-2-OL

FORMULA I, R_1 = H, R = Br, R_2 = tert.-butyl, R_3 = H, n = 2, m = 0

The procedure of Example 12 is followed, but using 10 g of 3-[o-bromo-p-(tetrahydrofuranyl-3')]-phenoxy-1,2-epoxy-propane obtained in Example 46 and 30 cm^3 of tert.-butylamine. After recrystallisation from isopropanol, 8 g of the hydrochloride of 1-[o-bromo-p-(tetrahydrofuranyl-3')]-phenoxy-3-tert.-butylamino-propan-2-ol are recovered in the form of white crystals of melting point 144-47°C.

EXAMPLE 49

4-(p-HYDROXYBENZOYL)-BUTYRIC ACID

FORMULA VI, R = H, n = 3

* Translator's note: No quantity given

The procedure of Example 1 is followed, but starting from 85 g of 4-(p-methoxybenzoyl)-butyric acid, prepared by the Friedel-Crafts reaction of glutaric anhydride with anisole. 31 g of 4-(p-hydroxybenzoyl)-butyric acid are obtained in the form of crystals of melting point 190-5°C.

EXAMPLE 50

ETHYL ESTER OF 4-(p-HYDROXYBENZOYL)-BUTYRIC ACID

FORMULA IV', R = H, n = 3

A solution of 31 g of 4-(p-hydroxybenzoyl)-butyric acid obtained in Example 49, in 250 cm^3 of ethanol containing 2 cm^3 of concentrated sulphuric acid, is heated under reflux for 6 hours.

The solution is then concentrated in vacuo, the residue is taken up in methylene chloride and the solution is washed with water and dried over sodium sulphate. After evaporating the solvent, the residue crystallises and the crystals are washed with pentane. 30 g of the ethyl ester of 4-(p-hydroxybenzoyl)-butyric acid are thus isolated in the form of white crystals of melting point 75-78°C.

EXAMPLE 51

2-(p-HYDROXYPHENYL)-TETRAHYDROPYRANE

FORMULA III, R_1 = R = H, n = 3, m = 0

The procedure of Example 14 is followed, but starting from 30 g of the ethyl ester of 4-(p-hydroxybenzoyl)-butyric acid obtained in Example 50. After filtration over silica gel, the eluant being a 9/1 mixture of methylene chloride and ether, 12 g of 2-(p-hydroxyphenyl)-tetrahydro-

pyrane are recovered in the form of white crystals of melting point 81-83°C.

EXAMPLE 52

3-[p-(TETRAHYDROPYRANYL-2')]-PHENOXY-1,2-EPOXY-PROPANE

FORMULA II, R_1 = R = H, Y = $-CH-CH_2$ (with O), n = 3, m = 0

The procedure of Example 9 is followed, but using 11.5 g of 2-(p-hydroxyphenyl)-tetrahydropyrane obtained in Example 51. 14 g of 3-[p-(tetrahydropyranyl-2')]-phenoxy-1,2-epoxy-propane are recovered in the form of an oil, which is used in the crude form for the next stage.

EXAMPLE 53 *

1-[p-(TETRAHYDROPYRANYL-2')]-PHENOXY-3-ISOPROPYLAMINO-PROPAN-2-OL

FORMULA I, R_1 = R = H, R_2 = isopropyl, R_3 = H, n = 3, m = 0

The procedure of Example 5 is followed, but using 14 g of 3-[p-(tetrahydropyranyl-2')]-phenoxy-1,2-epoxy-propane obtained in Example 52 and 30 cm^3 of isopropylamine. After crystallisation from pentane, 10.7 g of 1-[p-(tetrahydropyranyl-2')]-phenoxy-3-isopropylamino-propan-2-ol are recovered in the form of white crystals of melting point 67-68°C.

EXAMPLE 54

2-(p-Hydroxyphenyl)-4-methyl-tetrahydrofurane

(Formula III, R = H, R_1 = CH_3, n = 2, m = 0)

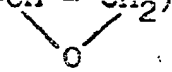
A solution of 26.5 g of the ethyl ester of 3-p-hydroxybenzoyl-2-methylpropionic acid in 110 cm^3 of tetrahydrofurane is added dropwise to a suspension of 6.3 g of the double hydride of aluminium and lithium in 110 cm^3 of tetrahydrofurane, the exothermic reaction being allowed to

develop and being controlled by the dropwise addition. The addition takes 1 hour 30 minutes after which the mixture is stirred for 3 hours and then left to stand overnight.

After cooling the reaction mixture, a little ethyl acetate is added, followed by cautious addition of a saturated aqueous sodium sulphate solution. When the hydride no longer reacts, the mixture is poured onto ice and hydrochloric acid, the organic products are then extracted with methylene chloride, the extract is dried and the solvent is evaporated. The residue obtained (19 g) is filtered over silica gel, the eluant being dichloromethane. 9 g of 2-(p-hydroxyphenyl)-4-methyl-tetrahydrofurane are thus recovered in the form of white crystals of melting point 118°C.

EXAMPLE 55

3-p-(4'-Methyl-tetrahydrofuranyl-2')-phenoxy-1,2-epoxy-propane

(Formula II, R = H, $R_1 = CH_3$, n = 2, m = 0, Y = )

A solution of 9 g of 2-(p-hydroxyphenyl)-4-methyl-tetrahydrofurane obtained in Example 54, 3.2 g of potassium hydroxide dissolved in 20 cm^3 of water and 10 cm^3 of epichlorohydrin in 150 cm^3 of ethanol is stirred for 24 hours at ambient temperature.

The reaction mixture is then concentrated in vacuo after which the residue is taken up in chloroform and the chloroform solution is washed with water, with a 5% strength sodium hydroxide solution and then again with water.

After having dried the chloroform phase, the solvent is evaporated and 10 g of 3-p-(4'-methyl-tetrahydrofuranyl-2')-phenoxy-1,2-epoxy-propane are obtained in the form of an oil which is used in the crude form for the next stage.

EXAMPLE 56

1-p-(4'-Methyl-tetrahydrofuranyl-2')-phenoxy-3-isopropyl-amino-propan-2-ol

(Formula I, R_3 = R = H, R_1 = CH_3, n = 2, m = 0, R_2 = isopropyl)

A mixture of 10 g of 3-p-(4'-methyl-tetrahydrofuranyl-2')-phenoxy-1,2-epoxy-propane obtained in Example 55 and of 20 cm^3 of isopropylamine is left for 48 hours in a stoppered flask at ambient temperature.

The reaction mixture is then concentrated in vacuo, the residue obtained is taken up in ether and the basic products are extracted with a 10% strength aqueous solution of hydrochloric acid.

The acid phase is rendered alkaline in the cold and the organic products are extracted with ether; the extract is dried and evaporated. The residue obtained crystallises from pentane. After recrystallisation from pentane, 4.2 g of 1-p-(4'-methyl-tetrahydrofuranyl-2')-phenoxy-3-isopropylamino-propan-2-ol are recovered in the form of white crystals of melting point 59-62°C.

EXAMPLE 57

1-(p-Benzyloxyphenyl)-3-furyl-prop-2-en-1-one

(Formula XII, R = R_1 = H, n = 2)

60 g of p-benzyloxyacetophenone and 24 g of furfural are dissolved hot in 150 cm^3 of ethanol. The solution is then cooled and 1.3 g of potassium hydroxide dissolved in 15 cm^3 of 95% strength ethanol are added. The reaction mixture is stirred at ambient temperature for 3 hours and 150 g of ice are then added. The crystals formed are filtered off, washed with water and dried. 78 g of 1-p-(benzyloxyphenyl)-3-furyl-prop-2-en-1-one are thus recovered in the form of crystals of melting point 114°C.

EXAMPLE 58

1-(p-Hydroxyphenyl)-3-(tetrahydrofuranyl-2')-propane

(Formula III, $R_1 = R = H$, $n = 2$, $m = 3$)

A solution of 78 g of 1-p-(benzyloxyphenyl)-3-furyl-prop-2-en-1-one obtained in Example 57, in 400 cm^3 of methanol, is subjected to hydrogenation for 7 hours at 70 kg[M] of hydrogen at 120°C in the presence of Raney Ni which has beforehand been washed with a 10% strength hydrochloric acid solution and then twice with water.

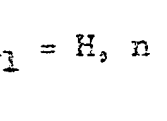
The reaction mixture is then filtered and concentrated in vacuo, and the residue is taken up in methylene chloride. The organic phase is extracted with a 10% strength potassium hydroxide solution. The alkaline-aqueous phase is acidified cold with hydrochloric acid and the organic products are extracted with ether. The ether phase is washed with water and then dried, and the ether is evaporated in vacuo. 13 g of 1-(p-hydroxyphenyl)-3-(tetrahydrofuranyl-2')-propane are thus recovered in the form of a thick oil which is used, in the form in which it

[M] Sic - ? 70 kg pressure - if so, kg per what?

is obtained, for the subsequent operations.

EXAMPLE 59

3-{p-[3-(Tetrahydrofuranyl-2')-propyl]-phenoxy}-1,2-epoxy-propane

(Formula II, R = R_1 = H, n = 2, m = 3, Y = )

The procedure of Example 55 is followed, but using 11.5g of 1-(p-hydroxyphenyl)-3-(tetrahydrofuranyl-2')-propane obtained in Example 58. 14 g of 3-{p-[3-(tetrahydrofuranyl-2')-propyl]-phenoxy}-1,2-epoxy-propane are recovered in the form of an oil which is used in the crude form for the next stage.

EXAMPLE 60 *

1-{p-[3-(Tetrahydrofuranyl-2')-propyl]-phenoxy}-3-isopropyl-amino-propan-2-ol

(Formula I, R = R_1 = R_3 = H, n = 2, m = 3, R_2 = isopropyl)

A solution of 14 g of 3-{p-[3-(tetrahydrofuranyl-2')-propyl]-phenoxy}-1,2-epoxy-propane obtained in Example 59 and of 30 cm^3 of isopropylamine in 30 cm^3 of isopropanol is heated for 7 hours at 120-130°C in a sealed tube.

The reaction mixture is then concentrated in vacuo after which it is taken up with 10% strength hydrochloric acid. The neutral products are extracted three times with ether.

The aqueous phase is then cooled to 0°C and rendered alkaline, in the cold, by means of a 10% strength aqueous sodium hydroxide solution. The aminoalcohol is extracted with chloroform and the extract is washed with water, dried over sodium carbonate and decolorised with active charcoal.

After filtration and evaporation of the solvent, 7.5 g of an oily residue are recovered. The maleate is produced from this oily residue by adding maleic acid dissolved in acetone. The salt crystallises from a mixture of acetone and ether. The crystals are filtered off, washed with a mixture of acetone and ether and then dried. 8.2 g of 1-{p-[3-(tetrahydrofuranyl-2')-propyl]-phenoxy}-3-isopropyl-amino-propan-2-ol are thus recovered in the form of white crystals of the maleate of melting point 127-129°C.

EXAMPLE 61

Furyl-2 p-methoxyphenyl ketone

(Formula XIV, R_1 = R = H, n = 2, m = 1)

A mixture of 270 g of furane-2-carboxylic acid, 340 g of anisole and 2 kg of polyphosphoric acid is stirred for 4 hours at 55°C. The reaction mixture is then poured onto ice and the organic products are extracted with ether, and the extract is washed carefully with water, with a 5% strength sodium hydroxide solution and again with water, and is dried. After evaporating the solvent, the oily residue obtained is subjected to a distillation in vacuo. 262 g of furyl-2 p-methoxyphenyl ketone are thus recovered in the form of white crystals.

Boiling point$_{2\ mm\ Hg}$ = 160-168°C, melting point = 56-8°C.

EXAMPLE 62

Furyl-2 p-hydroxyphenyl ketone

(Formula XIII, R_1 = R = H, n = 2, m = 1)

A mixture of 30 g of furyl-2 p-methoxyphenyl ketone

obtained in Example 61 and of 90 g of pyridine hydrochloride is heated at 210°C for 1 hour. The reaction mixture is then poured onto ice and the precipitate formed is filtered off. This precipitate is then taken up in a 5% strength potassium hydroxide solution. The alkaline aqueous solution is carefully washed with ether and then acidified in the cold. The crystals obtained are then filtered off and dried.

16.5 g of furyl-2 p-hydroxyphenyl ketone are thus obtained in the form of white crystals of melting point 163°C.

EXAMPLE 63

p-Furfurylphenol

(Formula XI, $R_1 = R = H$, $n = 2$, $m = 1$)

A solution of 14.5 g of furyl-2 p-hydroxyphenyl ketone obtained in Example 62, in 65 cm^3 of water containing 6 g of potassium hydroxide, is heated to 70-80°C.

12 g of potassium borohydride are gently added to this solution by means of a spatula. The reaction mixture is then heated on a boiling water bath for 4 hours.

Thereafter it is poured onto ice, and then acidified at 0°C by means of 10% strength hydrochloric acid. The organic products are then extracted with ether and the extract is washed with water and dried. The 12 g of oily residue which is obtained is distilled in vacuo. 9 g of p-furfurylphenol are thus recovered in the form of white crystals.

Boiling point$_{7\ mm\ Hg}$ = 135 - 138°C. Melting

point below 50°C.

EXAMPLE 64

p-Tetrahydrofurfurylphenol

(Formula III, R_1 = R = H, n = 2, m = 1)

A solution of 10 g of p-furfurylphenol obtained in Example 63, in 100 cm^3 of water containing 2.6 g of sodium hydroxide, are subjected to hydrogenation in the presence of 2 g of Raney Ni for 1 hour 15 minutes at 50 kg* of hydrogen. The reaction mixture is then filtered to separate off the catalyst and the filtrate is extracted with ether. The aqueous alkaline phase is acidified at 0°C by means of 10% strength hydrochloric acid and the organic products are extracted with ether. The ether phase is washed with water and dried. The ether is evaporated in vacuo and the oily residue, amounting to 8 g, is subjected to a vacuum distillation. 5 g of p-tetrahydrofurfurylphenol are thus recovered in the form of a colourless oil.

Boiling point$_{3.5\ mm\ Hg}$ = 155 - 158°C.

EXAMPLE 65

3-p-Tetrahydrofurfurylphenoxy-1,2-epoxy-propane

(Formula II, R = R_1 = H, n = 2, m = 1, Y = $-CH - CH_2$ with O bridging)

The procedure of Example 55 is followed, but using 5 g of p-tetrahydrofurfurylphenol obtained in Example 64, 5.8 g of 3-p-tetrahydrofurfurylphenoxy-1,2-epoxy-propane are recovered in the form of an oil which is used in the crude state for the next stage.

* Sic - ? 50 kg pressure - if so, kg per what?

EXAMPLE 66 *

1-p-Tetrahydrofurfurylphenoxy-3-isopropylamino-propan-2-ol

(Formula I, R = R_1 = R_3 = H, n = 2, m = 1, R_2 = isopropyl)

The procedure of Example 56 is followed, but using 2.5 g of 3-p-tetrahydrofurfurylphenoxy-1,2-epoxy-propane obtained in Example 65. 2.4 g of 1-p-tetrahydrofurfuryl-phenoxy-3-isopropylamino-propan-2-ol are recovered in the form of white crystals of melting point 58-60°C.

EXAMPLE 67

o-Bromo-p-tetrahydrofurfurylphenol

(Formula III, R_1 = H, R = Br, n = 2, m = 1)

8.5 g of N-bromosuccinimide are added in small portions, by means of a spatula, to a solution of 8 g of p-tetrahydrofurfurylphenol obtained in Example 64 in 100 cm^3 of dimethylformamide, cooled with a mixture of water and ice. At the end of the addition, the mixture is allowed to return to ambient temperature after which it is stirred for 6 hours and left to stand overnight. Water and ice are then added to the reaction mixture and the organic products are extracted with ether. The ether phase is washed with water and dried. After evaporation of the ether, a residue of 10 g is obtained. This residue is taken up in a mixture of ether/acetone/petroleum ether. The insoluble product which separates out (1.2 g), corresponding to the o-dibromo-p-tetrahydrofurfurylphenol derivative (melting point = 143-147°C) is filtered off. The filtrate is evaporated in vacuo and the residue crystallises. After recrystallisation of the crystals obtained from isopropyl

ether, 4.5 g of o-bromo-p-tetrahydrofurfurylphenol are recovered in the form of white crystals of melting point 89-91°C.

EXAMPLE 68

3-o-Bromo-p-tetrahydrofurfurylphenoxy-1,2-epoxy-propane

(Formula II, R_1 = H, R = Br, n = 2, m = 1, Y = -CH - CH_2 with O)

The procedure of Example 55 is followed, but using 4.5 g of o-bromo-p-tetrahydrofurfurylphenol obtained in Example 67. 5 g of 3-o-bromo-p-tetrahydrofurfurylphenoxy-1,2-epoxy-propane are recovered in the form of an oil, which is used in the crude state for the next stage.

EXAMPLE 69 *

1-o-Bromo-p-tetrahydrofurfurylphenoxy-3-tert.-butylamino-propan-2-ol

(Formula I, R_1 = R_3 = H, R = Br, n = 2, m = 1, R_2 = tert.-butyl)

The procedure of Example 56 is followed, but using 5 g of 3-o-bromo-p-tetrahydrofurfurylphenoxy-1,2-epoxy-propane obtained in Example 68 and 10 cm^3 of tert.-butylamine. An oil is recovered, which is dissolved in ether, and a solution of hydrogen chloride in ether is added. The hydrochloride formed, which crystallises, is filtered off, washed with ether and then recrystallised from isopropanol. 4 g of 1-o-bromo-p-tetrahydrofurfurylphenoxy-3-tert.-butylamino-propan-2-ol are thus recovered in the form of white crystals of hydrochloride, of melting point 164-166°C.

EXAMPLE 70

2-(4-Hydroxy-3-chloro-phenyl)-4-methyl-tetrahydrofurane

(Formula III, R = Cl, $R_1 = CH_3$, n = 2, m = 0)

15.8 g of N-chlorosuccinimide dissolved in 80 cm^3 of dimethylformamide are added in small portions to a solution of 21 g of 2-(p-hydroxyphenyl-4-methyl-tetrahydrofurane obtained in Example 54 in 210 cm^3 of dimethylformamide, cooled with a mixture of water and ice. At the end of the addition, the mixture is allowed to return to ambient temperature after which it is stirred for 8 hours and left to stand for 24 hours. Water and ice are then added to the reaction mixture and the organic products are extracted with ether. The ether phase is washed with water and dried. After evaporation of the ether, a residue of 24.6 g is obtained. This residue is triturated in an ether/pentane mixture and the crystals formed are dried and then recrystallised from isopropyl ether. 14.4 g of 2-(4-hydroxy-3-chloro-phenyl)-4-methyl-tetrahydrofurane are thus recovered in the form of white crystals of melting point 101-103°C.

EXAMPLE 71

3-[o-Chloro-p-(4'-methyl-tetrahydrofuranyl - 2')]-phenoxy-1,2-epoxy-propane

(Formula II; R = Cl, $R_1 = CH_3$, n = 2, m = 0, Y = $-CH-CH_2$ with O)

A solution of 4.3 g of 2-(4-hydroxy-3-chloro-phenyl)-4-methyl-tetrahydrofurane obtained in Example 70, 1.5 g of potassium hydroxide dissolved in 10 cm^3 of water and 7.5 cm^3 of epichloro-

hydrin in 75 cm^3 of ethanol is stirred for 24 hours at ambient temperature.

The reaction mixture is then concentrated in vacuo after which the residue is taken up in chloroform and the chloroform solution is washed with water, with a 5% strength sodium hydroxide solution and then again with water. After having dried the chloroform phase, the solvent is evaporated and 5.2 g of 3-[o-chloro-p-(4'-methyl-tetrahydrofuranyl-2')]-phenoxy-1,2-epoxy-propane are obtained in the form of an oil which is used in the crude form for the next stage.

EXAMPLE 72 *

Hydrochloride of 1-[o-chloro-p-(4'-methyl-tetrahydrofuranyl-2')]-phenoxy-3-isopropylamino-propan-2-ol

(Formula I, R = Cl, $R_1 = CH_3$, $R_3 = H$, n = 2, m = 0 R_2 = isopropyl)

A mixture of 6.5 g of 3-[o-chloro-p-(4'-methyl-tetrahydrofuranyl-2')]-phenoxy-1,2-epoxy-propane obtained in Example 71 and 15 cm^3 of isopropylamine is left for 48 hours in a stoppered flask at ambient temperature.

The reaction mixture is then concentrated in vacuo, the residue obtained is taken up in ether and the basic products are extracted with a 10% strength aqueous solution of hydrochloric acid.

The acid phase is rendered alkaline in the cold and the organic products are extracted with ether; the extract is dried and evaporated. The oily residue of 6 g obtained is dissolved in 50 cm^3 of ether and ethyl chloride is added in the cold until an acid pH is reached. The crystals obtained are then dried and washed carefully with ether. After drying,

5.7 g of the hydrochloride of 1-[o-chloro-p-(4'-methyl-tetrahydrofuranyl-2')]-phenoxy-3-isopropylamino-propan-2-ol are recovered in the form of white crystals of melting point 102-104°C.

EXAMPLE 73 *

Maleate of 1-[o-chloro-p-(4'-methyl-tetrahydrofuranyl-2')]-phenoxy-3-tert.-butylamino-propan-2-ol

(Formula I, R = Cl, R_1 = CH_3, R_3 = H, n = 2, m = 0, R_2 = tertiary butyl)

Following the procedure in Example 72, but using 5.2 g of 3-[o-chloro-p-(4'-methyl-tetrahydrofuranyl-2')]-phenoxy-1,2-epoxy-propane obtained in Example 71 and 15 cm^3 of tert.-butylamine, 5.7 g of base are recovered in the form of an oily residue. The maleate is formed from this residue by adding maleic acid in an ether/acetone mixture. After having washed with ether and dried the crystals formed, 6.1 g of the maleate of 1-[o-chloro-p-(4'-methyl-tetrahydrofuranyl-2')]-phenoxy-3-tert.-butylamino-propan-2-ol are recovered in the form of white crystals of melting point 91-94°C.

EXAMPLE 74

o-Chloro-p-tetrahydrofurfuryl-phenol

(Formula III, R_1 = H, R = Cl, n = 2, m = 1).

Following the procedure in Example 70, but using 20 g of p-tetrahydrofurfuryl-phenol obtained in Example 64, after re-crystallisation from an isopropyl ether/pentane mixture 17.2 g of o-chloro-p-tetrahydrofurfuryl-phenol are obtained in the form of white crystals of melting point 54-57°C.

EXAMPLE 75

3-o-Chloro-p-tetrahydrofurfurylphenoxy-1,2-epoxy-propane

(Formula II, R_1 = H, R = Cl, n = 2, m = 1, Y = $-CH-CH_2$ with O)

The procedure of Example 71 is followed, but using 8.6 g of o-chloro-p-tetrahydrofurfuryl-phenol obtained in Example 74. 10 g of 3-o-chloro-p-tetrahydrofurfurylphenoxy-1,2-epoxy-propane are recovered in the form of an oil, which is used in the crude state for the next stage.

EXAMPLE 76 *

Hydrochloride of 1-o-chloro-p-tetrahydrofurfurylphenoxy-3-isopropylamino-propan-2-ol

(Formula I, R_1 = R_3 = H, R = Cl, n = 2, m = 1, R_2 = isopropyl)

Following the procedure in Example 72, but using 10 g of 3-o-chloro-p-tetrahydrofurfurylphenoxy-1,2-epoxy-propane obtained in Example 75 and 20 cm^3 of isopropylamine, the base is recovered in the form of an oily residue. This residue is dissolved in 50 cm^3 of ether and ethyl chloride is added in the cold until an acid pH is reached. The crystals obtained are then dried and washed carefully with ether. After drying, 9.3 g of the hydrochloride of 1-o-chloro-p-tetrahydrofurfuryl-phenoxy-3-isopropylamino-propan-2-ol are recovered in the form of white crystals of melting point 99-100°C.

EXAMPLE 77 *

Hydrochloride of 1-o-chloro-p-tetrahydrofurfurylphenoxy-3-tert.-butylamino-propan-2-ol

(Formula I, R_1 = R_3 = H, R = Cl, n = 2, m = 1, R_2 = tert.-butyl)

Following the procedure in Example 72, but using 8 g of 3-o-chloro-p-tetrahydrofurfurylphenoxy-1,2-epoxy-propane obtained in Example 75 and 15 cm^3 of tert.-butylamine, the base is recovered

in the form of an oily residue. This oily residue is dissolved in 50 cm^3 of ether and ethyl chloride is added in the cold until an acid pH is reached. The crystals obtained are then dried and washed carefully with ether. After drying, 5.2 g of the hydrochloride of 1-o-chloro-p-tetrahydrofurfuryl-phenoxy-3-tert.-butylamino-propan-2-ol are recovered in the form of white crystals of melting point 128-131°C.

EXAMPLE 78 *

Maleate of 1-p-tetrahydrofurfurylphenoxy-3-tert.-butylamino-propan-2-ol

(Formula I, $R_1 = R_3 = R = H$, $n = 2$, $m = 1$, R_2 = tert.-butyl)

Following the procedure in Example 72 but using 12 g of 3-p-tetrahydrofurfurylphenoxy-1,2-epoxy-propane obtained in Example 65 and 20 cm^3 of tert.-butylamine, the base is recovered in the form of an oily residue. The maleate is formed from this residue by adding maleic acid in an acetone/ether mixture. After having dried and washed the crystals formed with ether, 11 g of the maleate of 1-p-tetrahydrofurfurylphenoxy-3-tert.-butylamino-propan-2-ol are recovered in the form of white crystals of melting point 144-147°C.

EXAMPLE 79

5-Methyl-furyl-2 p-methoxyphenyl ketone

(Formula XIV, $R_1 = CH_3$, $R = H$, $n = 2$, $m = 1$)

The magnesium compound of 4-bromoanisole is prepared starting from 150 g of 4-bromoanisole and 20 g of magnesium in 400 cm^3 of anhydrous tetrahydrofurane. A solution of 75 g of 5-methyl-furyl-2-nitrile in 100 cm^3 of tetrahydrofurane is added dropwise to this solution of the magnesium compound, whilst

stirring. After the end of the addition, the mixture is stirred for 1 hour at the laboratory temperature and then for 4 hours under reflux.

The reaction mixture is subsequently cooled and then ice and 300 cm^3 of 20% strength sulphuric acid are added. It is subsequently stirred for 1 hour at the laboratory temperature and then for 2 hours 30 minutes at 60°C.

After cooling and adding water, the mixture is extracted with ether and the ether extract is washed with water and dried over sodium sulphate. After evaporating the ether, the residue of 127 g obtained is subjected to distillation in vacuo. 96 g of 5-methyl-furyl-2 p-methoxyphenyl ketone are thus recovered in the form of a colourless oil.

Boiling point$_{2\ mm\ Hg}$ = 205-215°C.

EXAMPLE 80

5-Methyl-furyl-2 p-hydroxyphenyl ketone

(Formula XIII, $R_1 = CH_3$, R = H, n = 2, m = 1)

96 g of aluminium chloride are added gently, with a spatula, to a solution of 96 g of 5-methyl-furyl-2 p-methoxyphenyl ketone obtained in Example 79 in 150 cm^3 of chlorobenzene. After the end of the addition, the reaction mixture is heated to 130°C for 1 hour. It is then cooled, water and chloroform are added and the organic phase is separated off.

This organic phase is then extracted with a 10% strength potassium hydroxide solution.

The basic phase is then acidified in the cold and the precipitate formed is dried and washed with water.

After drying, 84 g of 5-methyl-furyl-2 p-hydroxyphenyl

ketone are recovered in the form of white crystals of melting point 201°C.

EXAMPLE 81

p-(5-Methyl-furfuryl)-phenol

(Formula XI, $R_1 = CH_3$, R = H, n = 2, m = 1)

A solution of 84 g of 5-methyl-furyl-2 p-hydroxyphenyl ketone obtained in Example 80 in 830 cm^3 of water containing 46.5 g of potassium hydroxide is brought to 70-80°C.

45 g of potassium borohydride are added gently, with a spatula, to this solution. The reaction mixture is then heated on a boiling water bath for 1 hour 30 minutes.

It is subsequently cooled, poured onto ice and then acidified at 0°C with 10% strength hydrochloric acid. The organic products are extracted with ether and the extract is washed with water and dried. After evaporating the solvent, the oily residue of 85 g obtained is distilled in vacuo. 50.7 g of p-(5-methyl-furfuryl)-phenol are thus recovered in the form of an oil.

Boiling point$_{1\ mm\ Hg}$ = 130-135°C.

EXAMPLE 82

p-(5-Methyl-tetrahydrofurfuryl)-phenol

(Formula III, $R_1 = CH_3$, R = H, n = 2, m = 1)

A solution of 50.7 g of p-(5-methyl-furfuryl)-phenol obtained in Example 81 in 200 cm^3 of water containing 19.5 g of sodium hydroxide is subjected to hydrogenation for 1 hour 15 minutes under 50 kg of hydrogen and at 110°C in the presence of 10 g of Raney Ni. The reaction mixture is then filtered in order to separate off the catalyst and the filtrate is extracted with

ether. The aqueous alkaline phase is acidified at 0°C with 10% strength hydrochloric acid and the organic products are extracted with ether. The ether phase is washed with water and dried, the ether is evaporated in vacuo and the oily residue is subjected to distillation in vacuo. 20 g of p-(5-methyl-tetrahydrofurfuryl)-phenol are thus recovered in the form of white crystals.

Boiling point$_{2\ mm\ Hg}$ = 160-175°C, melting point = 77°C.

EXAMPLE 83

3-p-(5-Methyl-tetrahydrofurfuryl)-phenoxy-1,2-epoxy-propane

(Formula II, $R_1 = CH_3$, R = H, n = 2, m = 1, Y = $-CH-CH_2$ with CH_2 bridging to O)

The procedure in Example 71 is followed but using 7 g of p-(5-methyl-tetrahydrofurfuryl)-phenol obtained in Example 82. 9 g of 3-p-(5-methyl-tetrahydrofurfuryl)-phenoxy-1,2-epoxy-propane are recovered in the form of an oil which is used in the crude state in the following stage.

EXAMPLE 84*

Maleate of 1-p-(5-methyl-tetrahydrofurfuryl)-phenoxy-3-isopropyl-amino-propan-2-ol

(Formula I, R = H, $R_1 = CH_3$, n = 2, m = 1, R_3 = H, R_2 = isopropyl)

Following the procedure in Example 72 but using 9 g of 3-p-(5-methyl-tetrahydrofurfuryl)-phenoxy-1,2-epoxy-propane obtained in Example 83 and 20 cm^3 of isopropylamine, the base is recovered in the form of an oily residue. The maleate is formed from this residue by adding maleic acid in an ether/acetone mixture. After recrystallisation from acetone of the crystals obtained, 5.8 g of the maleate of 1-p-(5-methyl-tetrahydrofurfuryl)-phenoxy-3-isopropylamino-propan-2-ol are recovered

in the form of white crystals of melting point 102-3°C.

EXAMPLE 85

o-Bromo-p-(5-methyl-tetrahydrofurfuryl)-phenol

(Formula III, $R_1 = CH_3$, R = Br, n = 2, m = 1)

Following the procedure in Example 70 but using 7.3 g of p-(5-methyl-tetrahydrofurfuryl)-phenol obtained in Example 82 and 6.8 g of N-bromosuccinimide, after recrystallisation from heptane 6.3 g of o-bromo-p-(5-methyl-tetrahydrofurfuryl)-phenol are obtained in the form of white crystals of melting point 101°C.

EXAMPLE 86

3-o-Bromo-p-(5-methyl-tetrahydrofurfuryl)-phenoxy-1,2-epoxy-propane

(Formula II, $R_1 = CH_3$, R = Br, n = 2, m = 1, Y = $-CH-CH_2$ with the epoxide oxygen)

The procedure in Example 71 is followed but using 6.3 g of o-bromo-p-(5-methyl-tetrahydrofurfuryl)-phenol obtained in Example 84. 7.3 g of 3-o-bromo-p-(5-methyl-tetrahydrofurfuryl)-phenoxy-1,2-epoxy-propane are recovered in the form of an oil which is used in the crude state in the following stage.

EXAMPLE 87

Maleate of 1-[o-bromo-p-(5-methyl-tetrahydrofurfuryl)-phenoxy]-3-tert.-butylamino-propan-2-ol

(Formula I, R = Br, $R_1 = CH_3$, n = 2, m = 1, R_3 = H, R_2 = tert.-butyl)

Following the procedure in Example 72 but using 7.3 g of 3-o-bromo-p-(5-methyl-tetrahydrofurfuryl)-phenoxy-1,2-epoxy-propane obtained in Example 86 and 20 cm^3 of tert.-butylamine, 7 g of the base are recovered in the form of an oily residue. The maleate is formed from this residue by adding maleic acid in

an ether/acetone mixture. The crystals obtained are dried and washed with ether. 7.7 g of the maleate of 1-[o-bromo-p-(5-methyl-tetrahydrofurfuryl)]-phenoxy-3-tert.-butylamino-propan-2-ol are thus recovered in the form of white crystals of melting point 85-88°C.

EXAMPLE 88

Furyl-2 4-methoxy-3-n-propyl-phenyl ketone

(Formula XIV, R_1 = H, R = n-propyl, n = 2, m = 1)

A solution of 56 g of furane-2-carboxylic acid chloride in 100 cm^3 of dichloromethane is added dropwise to a solution of 64 g of 2-n-propyl-1-methoxy-benzene in 600 cm^3 of dichloromethane containing, in suspension, 60 g of aluminium chloride, whilst cooling with a water/ice mixture. The reaction mixture is then stirred for 3 hours 30 minutes at the laboratory temperature. It is then poured onto a mixture of water and ice acidified with hydrochloric acid. The dichloromethane phase is subsequently decanted, washed with water, with a 5% strength sodium hydroxide solution and then with water again and is dried over sodium sulphate. After evaporating the solvent, the residue is subjected to distillation in vacuo. 112.5 g of furyl-2 4-methoxy-3-n-propyl-phenyl ketone are thus recovered in the form of a colourless liquid.

Boiling point$_{2\ mm\ Hg}$ = 175-190°C.

EXAMPLE 89

Furyl-2 4-hydroxy-3-n-propyl-phenyl ketone

(Formula XIII, R_1 = H, R = n-propyl, n = 2, m = 1)

Proceeding as in Example 80 but using 112.5 g of furyl-2 4-methoxy-3-n-propyl-phenyl ketone obtained in Example 88,

95.5 g of 2-furyl 4-hydroxy-3-n-propyl-phenyl ketone are recovered in the form of white crystals of melting point 102°C.

EXAMPLE 90

o-n-Propyl-p-furfuryl-phenol

(Formula XI, R_1 = H, R = n-propyl, n = 2, m = 1).

Following the procedure in Example 81 but using 95 g of 2-furyl 4-hydroxy-3-n-propyl-phenyl ketone obtained in Example 89, after distillation in vacuo 26 g of o-n-propyl-p-furfuryl-phenol are recovered in the form of a colourless oil.

Boiling point$_{2\ mm\ Hg}$ = 158-160°C.

EXAMPLE 91

o-n-Propyl-p-tetrahydrofurfuryl-phenol

(Formula III, R_1 = H, R = n-propyl, n = 2, m = 1)

A solution of 25.8 g of o-n-propyl-p-furfuryl-phenol obtained in Example 90 in 100 cm^3 of water containing 8.1 g of potassium hydroxide is subjected to hydrogenation for 16 hours under 40 kg of hydrogen and at ambient temperature in the presence of Raney Ni.

The reaction mixture is then filtered in order to separate off the catalyst and the filtrate is extracted with ether. The alkaline phase is acidified at 0°C with 10% strength hydrochloric acid and the organic products are extracted with ether. The ether phase is washed with water and dried, the ether is evaporated in vacuo and the oily residue of 25 g is subjected to distillation in vacuo. 21 g of o-n-propyl-p-tetrahydrofurfuryl-phenol are thus recovered in the form of a colourless oil.

Boiling point$_{2\ mm\ Hg}$ = 105°C.

EXAMPLE 92

3-[o-n-Propyl-p-tetrahydrofurfuryl]-phenoxy-1,2-epoxy-propane

(Formula II, R_1 = H, R = n-propyl, n = 2, m = 1, Y = $-CH-CH_2$ with O)

The procedure in Example 71 is followed but using 21 g of o-n-propyl-p-tetrahydrofurfuryl-phenol obtained in Example 91. 24.3 g of 3-[o-n-propyl-p-tetrahydrofurfuryl]-phenoxy-1,2-epoxy-propane are thus recovered in the form of an oil which is used in the crude state in the following stage.

EXAMPLE 93 *

Maleate of 1-[o-n-propyl-p-tetrahydrofurfuryl]-phenoxy-3-tert.-butylamino-propan-2-ol

(Formula I, R_1 = H, R = n-propyl, n = 2, m = 1, R_3 = H, R_2 = tert.-butyl)

Following the procedure in Example 72 but using 14.3 g of 3-[o-n-propyl-p-tetrahydrofurfuryl]-phenoxy-1,2-epoxy-propane obtained in Example 92 and 25 cm^3 of tert.-butylamine, 9.2 g of the base are recovered in the form of an oily residue. The maleate is formed from this residue by adding maleic acid in an acetone/ether mixture. After having dried the crystals formed and having washed them with ether, 10.9 g of the maleate of 1-[o-n-propyl-p-tetrahydrofurfuryl]-phenoxy-3-tert.-butylamino-propan-2-ol are recovered in the form of white crystals of melting point 106-108°C.

EXAMPLE 94 *

Hydrochloride of 1-[o-n-propyl-p-tetrahydrofurfuryl]-phenoxy-3-isopropylamino-propan-2-ol

(Formula I, R_1 = H, R = n-propyl, n = 2, m = 1, R_3 = H, R_2 = isopropyl)

Following the procedure in Example 72 but using 10 g of 3-[o-n-propyl-p-tetrahydrofurfuryl]-phenoxy-1,2-epoxy-propane obtained in Example 92 and 20 cm^3 of isopropylamine, 7.4 g of the base are recovered in the form of an oily residue. This residue is dissolved in 50 cm^3 of ether and ethyl chloride is added in the cold until an acid pH is reached. The crystals obtained are then dried and washed carefully with ether. After drying, 7.5 g of the hydrochloride of 1-[o-n-propyl-p-tetrahydrofurfuryl]-phenoxy-3-isopropylamino-propan-2-ol are recovered in the form of white crystals of melting point 108-111°C.

The pharmacological properties of the products according to the invention are demonstrated in the following texts:

I. CARDIOVASCULAR HAEMODYNAMICS IN DOGS

A) ACTION PROPER*

Method

Male or female mongrel dogs are anaesthetised with sodium mebubarbital (30 mg/kg given intravenously) and ventilated artificially by means of a Pesty RPP pump. They are given supplementary oxygen. The following are measured:

the systolic carotid pressure (A.P. syst.) and the diastolic carotid pressure (A.P. diast.),

the pulse rate (P.R.) and

the contractile force of the myocardium (Co. F).

The signals are amplified and recorded on a Beckman Dynograph. The following are calculated:

the mean arterial pressure (A.P. mean) = diastolic pressure + 0.43 (systolic pressure - diastolic pressure).

* ? intrinsic action

The products of the examples are injected into the ssphenous vein at doses of 0.125, 0.50, 2 and 4 mg/kg, dissolved in an aqueous 9°% (sic - ??) strength solution of sodium chloride.

Results

Table I shows the mean of the results obtained as a percentage variation relative to the initial value for the various cardiac parameters studied, for the products of each example.

TABLE I

Product from Example No.	Doses mg/kg given intra-venously	Mean pressure Δ %	Heart-beat Δ %	Contractile force Δ %	Duration of action in minutes
5	0.5	-6	-15	-15	5
	4.0	-27	-13	-27	>10
10	0.5	-13	-19	-11	10
	4.0	-55	-32	-45	>30
16	0.5	-6	-10	-17	5
	4.0	-11	-12	-20	25
43	0.5	-4	-15	-30	20
	4.0	-53	-15	-56	>30
44	0.5	-5	-11	-15	5
	4.0	-54	-10	-56	>30
30	0.5	-4	-6	-20	20
	4.0	-45	-9	-57	>30
20	0.5	-6	-6	-14	5
	4.0	-38	-10	-30	>30

TABLE I (continuation)

Product from Example No.	Doses mg/kg given intra-venously	Mean pressure Δ %	Heart-beat Δ %	Contractile force Δ %	Duration of action in minutes
17	0.5	-16	-14	-18	15
	4.0	-45	-10	-46	>30
21	0.5	-5	-2	-3	2
	4.0	-35	-5	-27	15
24	0.5	-4	-4	-6	5
	4.0	-30	-9	-32	15
35	0.5	-4	-12	-7	5
	4.0	-21	-24	-33	20
53	0.5	+2	+5	+3	2
	4.0	-49	-4	-35	20
36	0.5	-5	-8	-13	10
	4.0	-23	-9	-27	15
12	0.5	-6	-9	-13	15
	4.0	-42	-4	-39	>30
13	0.5	-8	-9	-7	5
	4.0	-32	-29	-27	20
25	0.5	-8	-3	-3	5
	4.0	-36	-7	-23	10
26	0.5	-5	-9	-7	5
	4.0	-43	-16	-26	20
27	0.5	-2	-5	-8	5
	4.0	-36	+24	-16	20
47	0.5	0	0	0	
	4.0	-40	-1	-36	25

TABLE I (continuation)

Product of Example No.	Doses mg/kg given intra-venously	Mean pressure Δ %	Heart-beat Δ %	Contractile force Δ %	Duration of action in minutes
48	0.5	-4	-11	-3	≥15
	4.0	-43	-9	-35	>30
60	0.5	-8	-4	-8	5
	4.0	-55	-5	-51	20
56	0.5	-6	-10	-6	3
	4.0	-43	-5	-35	20
66	0.5	-7	-10	-18	20
	4.0	-34	-4	-44	>40
69	0.5	-3	-4	-8	5
	2.0	-22	-5	-21	>20
72	0.5	-2	-10	-9	15
	4.0	-28	-11	-31	>20
73	0.5	-6	-10	-10	>15
	4.0	-32	-7	-25	>20
76	0.5	-6	-6	-9	15
	4.0	-39	-5	-34	>20
77	0.5	-6	-5	-4	15
	2.0	-36	-3	-26	>20
78	0.5	-9	-10	-16	>15
	4.0	-42	-8	-58	>30
84	0.5	-2	-6	-13	>15
	4.0	-35	-8	-43	>30
87	0.5	-4	-2	-10	15
	4.0	-33	-3	-33	30

TABLE I (continuation)

Product of Example No.	Doses mg/kg given intra-venously	Mean pressure Δ %	Heart-beat Δ %	Contractile force Δ %	Duration of action in minutes
93	0.5	-8	-5	-10	>15
	4.0	-46	-8	-37	>20
94	0.5	-4	-6	-6	>15
	4.0	-35	-8	-25	>20

B) β-BLOCKING ACTION

Method

The adrenergic β-blocking activity of the various examples was studied on the same dogs, in comparison with the β1 and β2 effects of isoprenaline.

The percentage inhibition of the β1 effects (increase in the myocardiac contractile force) and of the β2 effects (reduction in the diastolic arterial pressure) of isoprenaline is calculated as a function of the doses (mg/kg, given intravenously) of products of the various examples.

Results

Tables II and III which follow summarise the mean percentage inhibition of the β1 and β2 effects of isoprenaline, for the various products.

TABLE II

Percentage inhibition of the β_1 effects of isoprenaline

Product of Example No.	Doses in mg/kg (given intravenously)			
	0.125	0.5	2.0	4.0
5	+47	+77	+89	+95
10	+27	+62	+91	+97
16	+13	+43	+70	+86
43	+19	+47	+67	+70
44	0	+23	+55	+81
30	+32	+68	+85	+91
20	+43	+73	+86	+100
17	+9	+45	+82	+90
21	+85	+97	+100	+100
24	+26	+62	+88	+97
35	0	+19	+42	+44
53	+13	+45	+80	+90
36	+25	+55	+95	+100
12	+46	+72	+84	+90
13	+12	+32	+87	+93
25	+65	+96	+100	+100
26	+14	+31	+62	+89
27	0	0	0	+8
47	+66	+100	+100	+100

TABLE II (continuation)

Product of Example No.	Doses in mg/kg (given intravenously)				
	0.032	0.125	0.50	2.0	4.0
43	+30	+78	+100	+100	+100
60	+24	+47	+74	+90	+100
56	+42	+63	+92	+100	+100
66	+50	+78	+93	+95	+100
69	+78	+100	+100	+100	+100
72	+4	+38	+67	+92	+97
73	+28	+41	+76	+94	+97
76	+30	+60	+92	+97	+95
77	+57	+89	+99	+100	+100
78	+13	+37	+53	+70	+78
84	+9	+35	+63	+80	+100
87	+39	+85	+98	+100	+100
93	+29	+58	+86	+95	+96
94	+30	+62	+90	+95	+100

TABLE III

Percentage inhibition of the β_2 effects of isoprenaline

Product of Example No.	Doses in mg/kg (given intravenously)				
	0.032	0.125	0.50	2.0	4.0
5	-	+40	+18	+36	+18
10	-	+35	+18	+31	+44
16	-	+36	+36	+46	+57
43	-	+11	+17	+15	+8
44	-	0	+9	+9	+55
30	-	+10	+41	+50	+60

TABLE II (continuation)

Product of Example No.	Doses in mg/kg (given intravenously)				
	0.032	0.125	0.50	2.0	4.0
43	+30	+78	+100	+100	+100
60	+24	+47	+74	+90	+100
56	+42	+63	+92	+100	+100
65	+50	+78	+93	+95	+100
69	+78	+100	+100	+100	+100
72	+4	+38	+67	+92	+97
73	+28	+41	+76	+94	+97
76	+30	+60	+92	+97	+95
77	+57	+89	+99	+100	+100
78	+13	+37	+53	+70	+78
84	+9	+35	+63	+80	+100
87	+39	+85	+98	+100	+100
93	+29	+58	+86	+95	+96
94	+30	+62	+90	+95	+100

TABLE III

Percentage inhibition of the β_2 effects of isoprenaline

Product of Example No.	Doses in mg/kg (given intravenously)				
	0.032	0.125	0.50	2.0	4.0
5	-	+40	+18	+36	+18
10	-	+35	+18	+31	+44
16	-	+36	+36	+46	+57
43	-	+11	+17	+15	+8
44	-	0	+9	+9	+55
30	-	+10	+41	+50	+60

TABLE III (continuation)

Product of Example No.	Doses in mg/kg (given intravenously)				
	0.132	0.125	0.50	2.0	4.0
20	-	+15	+25	+29	+54
17	-	0	+10	+53	+36
21	-	+23	+42	+37	+53
24	-	+22	+19	+33	+36
35	-	+10	+29	+12	+31
53	-	+9	+9	+20	+39
36	-	+10	+20	+45	+50
12	-	+25	+45	+35	+50
13	-	+6	+15	+30	+49
25	-	+22	+16	+33	+60
26	-	+6	+13	+11	+5
27	-	+38	+21	0	0
47	-	+27	+34	+27	+41
48	+16	+25	+46	+66	+83
60	0	0	+3	+9	+15
56	+9	+7	+8	0	+5
66	+17	+24	+33	+57	+83
69	+33	+59	+72	+85	+77
72	+9	+11	+46	+31	+54
73	+10	+6	+13	+13	+13
76	0	0	+1	+18	+58
77	+20	+25	+44	+67	+83
78	0	+9	+13	+18	+78
84	+37	+37	+37	+22	+50
87	+15	+24	+21	+36	+67
93	+1	+6	+13	+48	+69
94	+12	+32	+71	+86	+92

II. TOXICITY

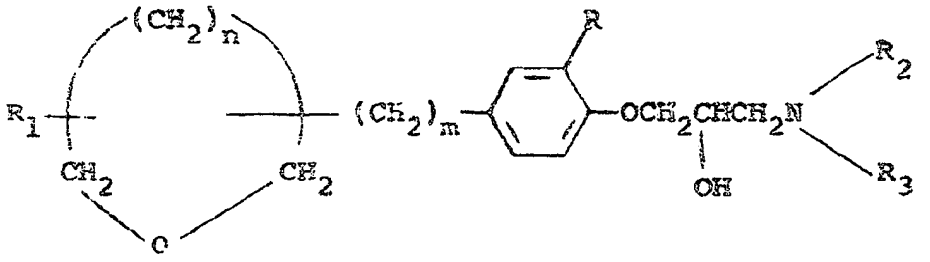
The 50% lethal dose in rats, of the products of the various examples, is between 64 and 256 mg/kg. These products were administered intraperitoneally.

In conclusion, the products of the examples exhibit a β1-blocking activity and can be administered as therapeutic agents for angina pectoris and arterial hypertension, at oral daily doses of 100 to 400 mg, or intravenous daily doses of 25 to 100 mg.

These products can be administered in doses of 25 and 100 mg in compressed tablets or in doses of 5 and 25 mg in ampoules containing an injectable solution.

The claims defining the invention are as follows:

1. A compound having the general formula:



I

in which

R_1 represents a hydrogen atom, a lower alkyl radical or a lower cycloalkyl radical,

R_2 and R_3 each represent a straight-chain or branched lower alkyl radical, or the dimethoxyphenylethyl or phenylisopropyl radical,

R_3 can also be a hydrogen atom,

R represents a hydrogen or halogen atom, or a lower alkyl, lower alkoxy, lower cycloalkyl, nitro, allyl or acetyl group,

n is equal to two or three, and

m is equal to zero, one, two or three,

and pharmaceutically acceptable non-toxic acid addition salts thereof.

2. A compound according to claim 1, wherein m is zero.

3. A compound according to claim 1 wherein m is one.

4. A compound according to claim 2 or 3, wherein R_1 is a hydrogen atom or a methyl or cyclopropyl radical, R_2 is an isopropyl or t-butyl radical or said dimethoxyphenylethyl or phenylisopropyl radical, R_3 is a hydrogen atom, and R is a hydrogen or halogen atom or an n-propyl, allyl, or methoxy radical.

5. 1-[p-(4'-Methyltetrahydrofuran-2-yl)-phenoxy]-3-isopropyaminopropan-2-ol.

6. 1-[o-Chloro-p-(methyl-4'-tetrahydrofuran-2-yl)-phenoxy]-3-isopropylaminopropan-2-ol.

7. 1-[o-Chloro-p-(methyl-4'-tetrahydrofuran-2-yl)-phenoxy]-3-t-butylaminopropan-2-ol.

8. 1-p-Tetrahydrofurfurylphenoxy-3-isopropylamino-propan-2-ol.

9. 1-[(p-Tetrahydrofurfuryl)phenoxy]-3-t-butyl-aminopropan-2-ol.

10. 1-o-Bromo-p-tetrahydrofurfuryiphenoxy-3-t-butylaminopropan-2-ol.

11. 1-[o-Chloro-p-(tetrahydrofurfuryl)phenoxy]-3-isopropylaminopropan-2-ol.

12. 1-[o-Chloro-p-(tetrahydrofurfuryl)-phenoxy]-3-t-butylaminopropan-2-ol.

13. 1-[o-n-Propyl-p-(tetrahydrofurfuryl)-phenoxy]-3-isopropylaminopropan-2-ol.

14. 1-[o-n-Propyl-p-(tetrahydrofurfuryl)-phenoxy]-3-t-butylaminopropan-2-ol.

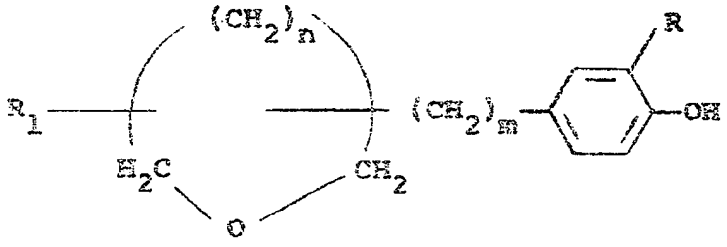
15. Any one of the compounds according to claim 1 hereinbefore specifically named, except those according to claims 4 to 14.

16. A pharmaceutically acceptable non-toxic acid addition salt of a compound according to any one of claims 4 to 14.

17. A salt according to claim 16 which is a hydrochloride or a maleate.

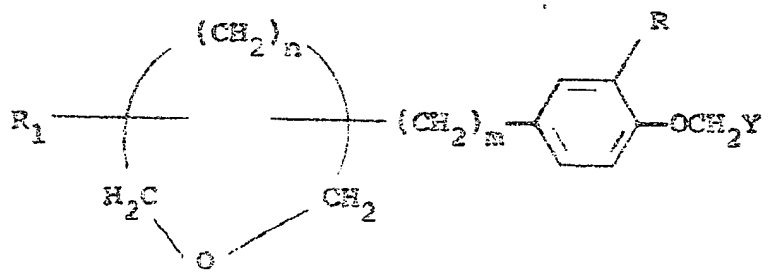
18. A process for preparing compounds having the general formula (I) as defined in claim 1, comprising the steps of

(a) reacting a phenol of general formula:



(III)

with an epihalogenohydrin to form a compound of general formula:



(II)

in which Y is the group $-CH-CH_2$ (O) or $-CH-CH_2X$ (OH), X being a

halogen atom.

and (b) reacting the compound of formula (II) with an amine of formula HNR_2R_3 in the presence or absence of organic solvent at a temperature between 20° and 150°C to form the compound of formula (I) which is then isolated and optionally converted into its non-toxic acid addition salt in a manner known per se.

19. A process for preparing a compound having the general formula (I) as defined in claim 1 or its non-toxic acid addition salt, substantially as described in any one of the foregoing Examples 5, 10, 12, 13, 16, 17, 20, 21, 24 to 27, 30, 35, 36, 43, 44, 47, 48, 53, 56, 60, 66, 69, 72, 73, 76, 77, 78, 84, 87, 93 and 94.

20. A compound having the general formula (I) as defined in claim 1 when prepared by a process according to claim 18 or 19.

21. A medicament having a adrenergic β-1 blocking effect, comprising at least one compound or salt according to any one of claims 1 to 17 and 20.

22. A pharmaceutical composition comprising as its active ingredient at least one compound or salt according to any one of claims 1 to 17 and 20, associated in a physiologically effective amount with a pharmaceutically acceptable carrier or diluent.

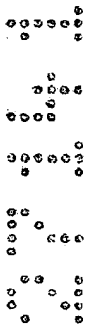
23. A composition according to claim 22 in a dosage form suitable for oral administration in doses of 25 to 100 mg.

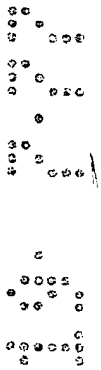
24. A composition according to claim 22 in a dosage form suitable for parenteral administration in doses of 5 to 25 mg.

DATED THIS 18th DAY OF JULY, 1977.

HEXACHIMIE.

Patent Attorneys for the Applicant.
F.B. RICE & CO.





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